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(54) Title: HUMAN TIMP-1 ANTIBODIES

(57) Abstract: Human antibodies that bind to TIMP-1 can be used as reagents to diagnose and treat disorders in which TIMP-1 is elevated, such as liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, colon cancer, lung cancer, and idiopathic pulmonary fibrosis.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/12801

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 16/00, 16/40
US CL : 530/388.26, 389.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/388.26, 389.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GUEDEZ et al. In vitro suppression of programmed cell death of B cells by tissue inhibitor of metalloproteinases-1. Journal of Clinical Investigation, December 1998, Vol. 102, No. 11, pages 2002-2010.	1-2,4-9, 23-24, 26 and 28
A	HOLTON-ANDERSEN et al. Measurement of the noncomplexed free fraction of tissue inhibitor of metalloproteinases 1 in plasma by immunoassay. Clinical Chemistry. August 2002, Vol. 48, No. 8, pages 1305-1313.	1-2,4-9, 23-24, 26 and 28

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z"

document member of the same patent family

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-2, 4-9, 23-24, 26 and 28

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

I. Claims 1, 2, 4-9, 23, 24, 26, and 28 drawn to a purified preparation of a human antibody, human TIMP-1 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

II. Claims 1, 10-15, 23, 27 and 28, drawn to a purified preparation of a human antibody, rat TIMP-1 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

III. Claims 1, 3, 23, 25 drawn to a purified preparation of a human antibody, rat TIMP-13 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

IV-CVIII. Claims 16-22, drawn to a purified preparation of a human antibody, TIMP-1 comprising VHCDR3 of SEQ ID NO:1-43, 360 and 140-182, VLCDR3 of SEQ ID NO: 44-86, 365-379, 97-139 or both amino acid sequence pair set forth in claims 18, 19, or 22, respectively.

CIX- CCXV Claims 29-52, drawn to a purified polynucleotide encoding VHCDR3 of SEQ ID NO:1-43, 360 and 140-182, VLCDR3 of SEQ ID NO: 44-86, 365-379, 97-139 or both amino acid sequence pair set forth in claims 18, 19, or 22, respectively, vectors and host cells.

CCXVI-CCLXVIII. Claims 54-63, drawn to a method of decreasing an MMP-inhibiting activity of a TIMP-1, wherein SEQ ID NO pair as set forth in claim 63, respectively.

CCLXVIII-CCCXXI Claims 64-68, drawn to a method of ameliorating symptoms of a disorder, wherein SEQ ID NO pair as set forth in claim 68, respectively.

CCCXXII- CCCLXXIV. Claims 69-72, drawn to a method of detecting a TIMP-1, wherein SEQ ID NO pair as set forth in claims 72, respectively.

CCCLXXV-CDXXVII. Claims 73-78, drawn to a method to aid in diagnosing a disorder, wherein SEQ ID NO pair as set forth in claim 76, respectively.

The inventions listed as Groups I-CDXXVII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I is a purified preparation of a human antibody, TIMP-1 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO:44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO:44.

The special technical feature of Group II, drawn to a purified preparation of a human antibody, rat TIMP-1 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

The special technical feature of Group III, drawn to a purified preparation of a human antibody, rat TIMP-13 comprising VHCDR3 of SEQ ID NO:1, VLCDR3 of SEQ ID NO: 44 or both amino acid sequence pair of SEQ ID NO:1 and SEQ ID NO: 44.

INTERNATIONAL SEARCH REPORT

PCT/US02/12801

The special technical feature of Groups IV-CVIII, drawn to a purified preparation of a human antibody, TIMP-1 comprising VHCDR3 of SEQ ID NO: 1-43, 360 and 140-182, VLCDR3 of SEQ ID NO: 44-86, 365-379, 97-139 or both amino acid sequence pair set forth in claims 18, 19, or 22, respectively.

The special technical feature of Groups CIX-CCXV, drawn to a purified polynucleotide encoding VHCDR3 of SEQ ID NO: 1-43, 360 and 140-182, VLCDR3 of SEQ ID NO: 44-86, 365-379, 97-139 or both amino acid sequence pair set forth in claims 18, 19, or 22, respectively, vectors and host cells.

The special technical feature of Groups CCXVI-CCLXVII, drawn to a method of decreasing an MMP-inhibiting activity of a TIMP-1, wherein SEQ ID NO pair as set forth in claim 63, respectively.

The special technical feature of Groups CCLXVIII-CCCXXI, drawn to a method of ameliorating symptoms of a disorder, wherein SEQ ID NO pair as set forth in claim 68, respectively.

The special technical feature of Groups CCCXXII-CCCLXXIV, drawn to a method of detecting a TIMP-1, wherein SEQ ID NO pair as set forth in claims 72, respectively.

The special technical feature of Groups CCCLXXV-CDXXVII, drawn to a method to aid in diagnosing a disorder, wherein SEQ ID NO pair as set forth in claim 76, respectively.

Accordingly, Groups I-CDXXVII are not so linked by the same or a corresponding special technical feature within meaning of PCT Rule 13.2 so as to form a single general inventive concept.

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(71) Applicants (for all designated States except US): **BAYER CORPORATION** [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US). **MORPHOSYS AG** [DE/DE]; Lena-Christ-Str. 48, 82152 Martinsried/München (DE).

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(75) Inventors/Applicants (for US only): **PAN, Clark** [US/US]; 22362 Princeton Place, Castro Valley, CA 94552 (US). **KNORR, Andreas, M.** [DE/DE]; Trillser Graben 10, 40699 Erkrath (DE). **SCHAUER, Michael** [DE/DE];

Falkenberg 28, 42113 Wuppertal (DE). **HIRTH-DIETRICH, Claudia** [DE/DE]; Stockmannsmühle 127, 42115 Wuppertal (DE). **KRAFT, Sabine** [DE/DE]; Planegger Strasse 11 A, 82152 Planegg (DE). **KREBS, Barbara** [DE/DE]; Auf Dem Kamm 13, 51427 Bergisch Gladbach (DE).

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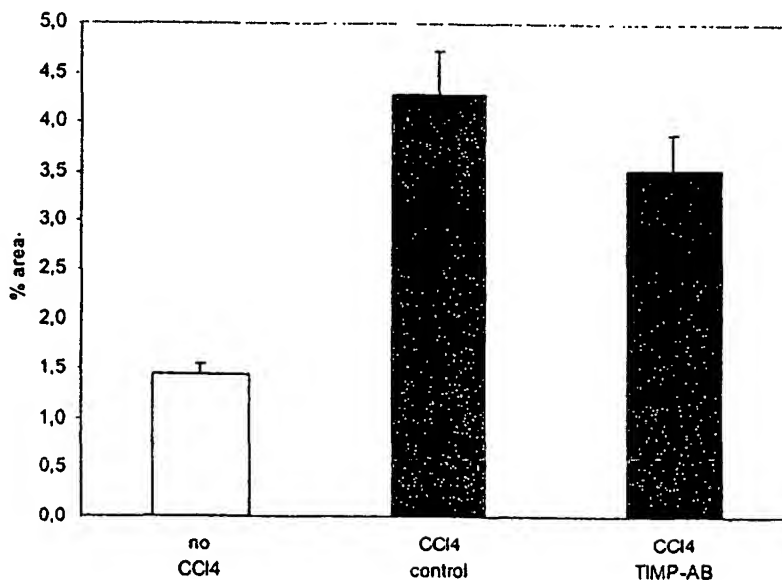
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[Continued on next page]

(54) Title: HUMAN TIMP-1 ANTIBODIES

Morphometry



(57) Abstract: Human antibodies that bind to TIMP-1 can be used as reagents to diagnose and treat disorders in which TIMP-1 is elevated, such as liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, colon cancer, lung cancer, and idiopathic pulmonary fibrosis.

WO 02/086085 A2



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NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

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HUMAN TIMP-1 ANTIBODIES

- [01] This application claims priority to and incorporates by reference co-pending provisional application Serial No. 60/285,683 filed April 24, 2001.

FIELD OF THE INVENTION

- [02] The invention relates to TIMP-1-binding human antibodies.

BACKGROUND OF THE INVENTION

- [03] Tissue inhibitors of metalloproteases (TIMPs) inhibit metalloproteases, a family of endopeptidase hydrolases. Metalloproteases are secreted by connective tissue and hematopoietic cells, use Zn^{2+} or Ca^{2+} for catalysis, and may be inactivated by metal chelators as well as TIMP molecules. Matrix metalloproteases (MMPs) participate in a variety of biologically important processes, including the degradation of many structural components of tissues, particularly the extracellular matrix (ECM).
- [04] Degradation of extracellular matrix tissue is desirable in processes where destruction of existing tissues is necessary, *e.g.*, in embryo implantation (Reponen *et al.*, *Dev. Dyn.* 202, 388-96, 1995), embryogenesis, and tissue remodeling. Imbalance between synthesis and degradation of matrix proteins, however, can result in diseases such as liver fibrosis (Iredale *et al.*, *Hepatology* 24, 176-84, 1996). This imbalance can occur, for example, if levels of TIMPs are increased. Disorders in which TIMP-1 levels of increased include, for example, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer. *See, e.g.*, Inokubo

et al., *Am. Heart J.* 141, 211-17, 2001; Ylisirnio *et al.*, *Anticancer Res.* 20, 1311-16, 2000; Holten-Andersen *et al.*, *Clin. Cancer Res.* 6, 4292-99, 2000; Holten-Andersen *et al.*, *Br. J. Cancer* 80, 495-503, 1999; Peterson *et al.*, *Cardiovascular Res.* 46, 307-15, 2000; Arthur *et al.*, *Alcoholism: Clinical and Experimental Res.* 23, 840-43, 1999; Iredale *et al.*, *Hepatol.* 24, 176-84, 1996.

- [06] There is a need in the art for reagents and methods of inhibiting TIMP-1 activity, which can be used to provide therapeutic effects.

BRIEF SUMMARY OF THE INVENTION

- [07] It is an object of the present invention to provide reagents and methods of inhibiting TIMP-1 activity. This and other objects of the invention are provided by one or more of the embodiments described below.
- [08] One embodiment of the invention is a purified preparation of a human antibody, wherein the antibody binds to a tissue inhibitor of metalloprotease-1 (TIMP-1) and neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.
- [09] Another embodiment of the invention is a purified preparation of a first human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.
- [10] Still another embodiment of the invention is a purified preparation of a first human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.
- [11] Yet another embodiment of the invention is a purified preparation of a first human antibody which has TIMP-1 binding and MMP-inhibiting activity characteristics of a second human antibody. The second antibody comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5

and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

- [12] Even another embodiment of the invention is a purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ

ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

- [13] A further embodiment of the invention is a purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101, SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NOS:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

- [14] Another embodiment of the invention is a pharmaceutical composition comprising a human antibody and a pharmaceutically acceptable carrier. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [15] Yet another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [16] Even another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [17] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [18] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
- [19] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID

NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

- [20] Yet another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.
- [21] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
- [22] Even another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.
- [23] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain

having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

- [24] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.
- [25] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [26] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
- [27] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

- [28] A further embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.
- [29] Another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
- [30] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.
- [31] Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human

antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

- [32] Even another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.
- [33] A further embodiment of the invention is a method of making a human antibody. The host cell of claim 43 is cultured under conditions whereby the antibody is expressed. The human antibody is purified from the host cell culture.
- [34] Another embodiment of the invention is a method of decreasing an MMP-inhibiting activity of a TIMP-1. The TIMP-1 is contacted with a human antibody that binds to the TIMP-1. The MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.
- [35] Still another embodiment of the invention is a method of ameliorating symptoms of a disorder in which TIMP-1 is elevated. An effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1 is administered to a patient having the disorder. Symptoms of the disorder are thereby ameliorated.
- [36] A further embodiment of the invention is a method of detecting a TIMP-1 in a test preparation. The test preparation is contacted with a human antibody that specifically binds to the TIMP-1. The test preparation is assayed for the presence of an antibody-TIMP-1 complex.

- [37] Even another embodiment of the invention is a method to aid in diagnosing a disorder in which a TIMP-1 level is elevated. A sample from a patient suspected of having the disorder is contacted with a human antibody that binds to TIMP-1. The sample is assayed for the presence of an antibody-TIMP-1 complex. Detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.
- [38] The invention thus provides human antibodies which bind to TIMP-1 and neutralize MMP-inhibiting activity of TIMP-1. These antibodies can be used, *inter alia*, in diagnostic and therapeutic methods.

BRIEF DESCRIPTION OF THE FIGURES

- [39] FIG. 1. Protein sequences encoded by the HuCAL[®] V_H and V_L Fab master genes. Seven V_H and V_L sequences are aligned, and the approximate location of restriction endonuclease sites introduced into the corresponding DNA sequences are indicated. The numbering is according to VBASE except for the gap in V_L position 9. In VBASE the gap is set at position 10. See also Chothia *et al.* (1992) *J. Mol. Biol.* 227, 776-798, Tomlinson *et al.* (1995) *EMBO J.* 14, 4628-4638 and Williams *et al.* (1996) *J. Mol. Biol.* 264, 220-232).
- [40] FIG. 2. Nucleotide sequences of the HuCAL[®] V_H and V_L Fab master genes.
- [41] FIG. 3. Fab display vector pMORPH[®] 18 Fab 1.
- [42] FIG. 4. Vector map of pMORPH[®] x9Fab1_FS.
- [43] FIG. 5. Sequence comparison between human and rat TIMP-1. Sequence regions in bold were used for peptide synthesis. Residues that make stronger direct contacts with MMP-3 are italicized, and residues that make weaker direct contacts with MMP-3 are underlined (Gomis-Ruth *et al.*, 1997).

- [44] FIG. 6. Activity of MS-BW-3 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (final conc. 50 μ M) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 27% MMP-1 activity (in absence of antibody) as reference values.
- [45] FIG. 7. Activity of MS-BW-44 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (final conc. 50 μ M) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 25% MMP-1 activity (in absence of antibody) as reference values.
- [46] FIG. 8. Activity of MS-BW-44, -44-2, 44-6 in human TIMP-1/ MMP-1 assay. Fab antibody fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 0.4 nM), MMP (final conc. 0.4 nM) and peptide substrate (final conc. 50 μ M) and incubation for 7 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 55% MMP-1 activity (in absence of antibody) as reference values.
- [47] FIG. 9. Activity of MS-BW-44, -44-2-4, 44-6-1 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 0.4 nM), MMP (final conc. 0.4 nM), and peptide substrate (final conc. 50 μ M) and incubation for 7 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in

material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 50% MMP-1 activity (in absence of antibody) as reference values.

- [48] FIG. 10. Binding of Fab fragments to human TIMP-1, -2, -3 and -4. TIMP-1, -2, -3, -4 proteins were immobilized on an ELISA plate, and binding of purified Fab fragments was measured by incubation with alkaline phosphatase conjugated anti-Fab antibody (Dianova) followed by development with Attophos substrate (Roche) and measurement at Ex405nm/Em535 nm.
- [49] FIG. 11. Activity of MS-BW-14, -17, -54 in rat TIMP-1/MMP-13 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (to final conc. 50 μ M) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-13 (in absence of TIMP-1) activity and 20% MMP-13 activity (in absence of antibody) as reference values.
- [50] FIG. 12. Activity of MS-BW-14 Fab and IgG₁ and MS-BW-3 IgG₁ in rat TIMP-1/ MMP-13 assay. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM) and peptide substrate (to final conc.50 μ M) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-13 activity (in absence of TIMP-1) and 30% MMP-13 activity (in absence of antibody) as reference values.
- [51] FIG. 13. Activity of MS-BW-17-1 Fab and IgG₁ in rat TIMP-1/ MMP-13 assay. Fab antibody fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM) and peptide substrate (to final conc.50 μ M) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as

outlined in material and methods section, using 100% MMP-13 activity (in absence of TIMP-1) and 15% MMP-13 activity (in absence of antibody) as reference values.

- [52] FIG. 14. Effect of the inhibitory effect of MS-BW-17-1 TIMP-1 antibody on bleomycin-induced lung fibrotic collagen.
- [53] FIG. 15. Effect of anti-TIMP-1 antibody on fibrotic collagen as stained by Sirius Red in carbon tetrachloride-induced rat liver fibrosis model. Sirius Red-stained area as percent of total field in carbon tetrachloride-treated rats treated with PBS, control antibody, and MS-BW-14 anti-TIMP-1 antibody.

DETAILED DESCRIPTION OF THE INVENTION

- [54] The invention provides human antibodies that bind to TIMP-1. These antibodies are useful for a variety of therapeutic and diagnostic purposes.

Characteristics of Human TIMP-1 Antibodies

- [55] "Antibody" as used herein includes intact immunoglobulin molecules (e.g., IgG₁, IgG_{2a}, IgG_{2b}, IgG₃, IgM, IgD, IgE, IgA), as well as fragments thereof, such as Fab, F(ab')₂, scFv, and Fv, which are capable of specific binding to an epitope of a human and/or rat TIMP-1 protein. Antibodies that specifically bind to TIMP-1 provide a detection signal at least 5-, 10-, or 20-fold higher than a detection signal provided with other proteins when used in an immunochemical assay. Preferably, antibodies that specifically bind to human and/or rat TIMP-1 do not detect other proteins in immunochemical assays and can immunoprecipitate the TIMP-1 from solution.
- [56] The K_d of human antibody binding to TIMP-1 can be assayed using any method known in the art, including technologies such as real-time Bimolecular Interaction Analysis (BIA) (Sjolander & Urbaniczky, *Anal. Chem.* 63, 2338-45, 1991, and Szabo *et al.*, *Curr. Opin. Struct. Biol.* 5, 699-705, 1995). BIA is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcoreTM).

Changes in the optical phenomenon surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

- [57] In a BIAcoreTM assay, some human antibodies of the invention specifically bind to human TIMP-1 with a K_d of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.2 nM to about 0.5 nM, about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM. More preferred human antibodies specifically bind to human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 M, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.
- [58] Other human antibodies of the invention specifically bind to rat TIMP-1 with a K_d of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM. Preferred K_d s range from about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.
- [59] Preferably, antibodies of the invention neutralize an MMP-inhibiting activity of the TIMP-1. The MMP can be, for example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-19, MMP-20 or MMP-23.
- [60] IC_{50} for neutralizing MMP-inhibiting activity of TIMP-1 can be measured by any means known in the art. Preferably, IC_{50} is determined using the high throughput fluorogenic assay described in Bickett *et al.*, *Anal. Biochem.* 212, 58-64, 1993. In a typical fluorogenic assay, the IC_{50} of a human antibody for neutralizing human TIMP-1 MMP-inhibiting activity ranges from about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM, and about 4 nM to about

11 nM. The IC_{50} for neutralizing human TIMP-1 MMP-inhibiting activity of some human antibodies is about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.

- [61] A typical IC_{50} for neutralizing rat TIMP-1 MMP-inhibiting activity ranges from about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3 nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM. The IC_{50} for neutralizing rat TIMP-1 MMP-inhibiting activity of some human antibodies is about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.
- [62] Preferred human antibodies of the invention are those for which the K_d for binding to TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the TIMP-1 are approximately equal.
- [63] A number of human antibodies having the TIMP-1 binding and MMP-inhibiting activity neutralizing characteristics described above have been identified by screening the MorphoSys HuCAL[®] Fab 1 library. The CDR cassettes assembled for the HuCAL[®] library were designed to achieve a length distribution ranging from 5 to 28 amino acid residues, covering the stretch from position 95 to 102. Knappik *et al.*, *J. Mol. Biol.* 296, 57-86, 2000. Some clones, however, had shorter VHCDR3 regions. In fact, it is a striking feature of anti-human TIMP-1 human antibodies identified from this library that they all exhibit the combination VH312 and a relatively short VHCDR3 region, typically four amino acids.
- [64] In some embodiments of the invention, the VHCDR3 region of a human antibody has an amino acid sequence shown in SEQ ID NOS:1-43. In other embodiments of the invention, the VLCDR3 region of a human antibody has an amino acid sequence shown in SEQ ID NOS:44-86. See Tables 2, 3, and 7. Human antibodies which have TIMP-1

binding and MMP-inhibiting activity neutralizing characteristics of antibodies such as those described above and in Tables 2, 3, and 7 also are human antibodies of the invention.

Obtaining human antibodies

- [65] Human antibodies with the TIMP-1 binding and MMP-activity neutralizing characteristics described above can be identified from the MorphoSys HuCAL[®] library as follows. Human or rat TIMP-1, for example, is coated on a microtiter plate and incubated with the MorphoSys HuCAL[®] Fab phage library (see Example 1, below). Those phage-linked Fabs not binding to TIMP-1 can be washed away from the plate, leaving only phage which tightly bind to TIMP-1. The bound phage can be eluted, for example, by a change in pH or by elution with *E. coli* and amplified by infection of *E. coli* hosts. This panning process can be repeated once or twice to enrich for a population of antibodies that tightly bind to TIMP-1. The Fabs from the enriched pool are then expressed, purified, and screened in an ELISA assay. The identified hits are then screened in the enzymatic assay described in Bickett *et al.*, 1993, and Bodden *et al.*, 1994. Those Fabs that lead to the degradation of the peptide are likely the ones which bind to TIMP-1, thereby blocking its interaction to MMP-1.
- [66] The initial panning of the HuCAL[®] Fab 1 library also can be performed with TIMP-1 as the antigen in round one, followed in round 2 by TIMP-1 peptides fused to carrier proteins, such as BSA or transferrin, and in round 3 by TIMP-1 again. Human TIMP-1 peptides which can be used for panning include human TIMP-1 residues 2-12 (TCVPPHPQTAF, SEQ ID NO:87; CTSVPPHPQTAF, SEQ ID NO:88; STCVPPHPQTAF, SEQ ID NO:89; STSVPPHPQTAF, SEQ ID NO:90), 28-36 (CEVNQTTLYQ, SEQ ID NO:91), 64-75 (PAMESVCGYFHR, SEQ ID NO:92), 64-79 (PAMESVCGYFHRSHNR, SEQ ID NO:93; CPAMESVSGYFHRSHNR, SEQ ID NO:94; PAMESVSGYFHRSHNRC, SEQ ID NO:95), and 145-157 (CLWTDQLLQGSE, SEQ ID NO:96). These peptide sequences are selected from

regions of human TIMP-1 that are predicted to interact with MMPs. See Gomis-Ruth *et al.*, *Nature* 389, 77-81, 1997. Directing Fabs toward the MMP-interacting region of human TIMP-1 in round 2 should increase the chance of identifying Fabs that can block the ability of human TIMP-1 to inhibit human MMP-1 activity.

- [67] Another method that can be used to improve the likelihood of isolating neutralizing Fabs is the panning on human TIMP-1 and eluting the binding Fabs with human MMP-1. This strategy should yield higher affinity antibodies than would otherwise be obtained.
- [68] Details of the screening process are described in the specific examples, below. Other selection methods for highly active specific antibodies or antibody fragments can be envisioned by those skilled in the art and used to identify human TIMP-1 antibodies.
- [69] Human antibodies with the characteristics described above also can be purified from any cell that expresses the antibodies, including host cells that have been transfected with antibody-encoding expression constructs. The host cells are cultured under conditions whereby the human antibodies are expressed. A purified human antibody is separated from other compounds that normally associate with the antibody in the cell, such as certain proteins, carbohydrates, or lipids, using methods well known in the art. Such methods include, but are not limited to, size exclusion chromatography, ammonium sulfate fractionation, ion exchange chromatography, affinity chromatography, and preparative gel electrophoresis. A preparation of purified human antibodies is at least 80% pure; preferably, the preparations are 90%, 95%, or 99% pure. Purity of the preparations can be assessed by any means known in the art, such as SDS-polyacrylamide gel electrophoresis. A preparation of purified human antibodies of the invention can contain more than one type of human antibody with the TIMP-1 binding and neutralizing characteristics described above.
- [70] Alternatively, human antibodies can be produced using chemical methods to synthesize its amino acid sequence, such as by direct peptide synthesis using solid-phase techniques (Merrifield, *J. Am. Chem. Soc.* 85, 2149-54, 1963; Roberge *et al.*, *Science* 269, 202-04,

1995). Protein synthesis can be performed using manual techniques or by automation. Automated synthesis can be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Optionally, fragments of human antibodies can be separately synthesized and combined using chemical methods to produce a full-length molecule.

- [71] The newly synthesized molecules can be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, PROTEINS: STRUCTURES AND MOLECULAR PRINCIPLES, WH Freeman and Co., New York, N.Y., 1983). The composition of a synthetic polypeptide can be confirmed by amino acid analysis or sequencing (e.g., using Edman degradation).

Assessment of therapeutic utility of human antibodies

- [72] To assess the ability of a particular antibody to be therapeutically useful to treat, liver fibrosis, for example, the antibody can be tested *in vivo* in a rat liver fibrosis model. Thus, preferred human antibodies of the invention are able to block both human and rat TIMP-1 activity. If desired, human Fab TIMP-1 antibodies can be converted into full immunoglobulins, for example IgG₁ antibodies, before therapeutic assessment. This conversion is described in Example 5, below.
- [73] To identify antibodies that cross-react with human and rat TIMP-1, an ELISA can be carried out using rat TIMP-1. Functional cross-reactivity can be confirmed in an enzymatic assay, as described in Bickett *et al.*, *Anal. Biochem.* 212, 58-64, 1993. The assay uses human or rat TIMP-1, human MMP-1 or rat MMP-13 (the rat counterpart of human MMP-1), and a synthetic fluorogenic peptide substrate. Enzyme activity of uncomplexed MMP-1 (or MMP-13) is assessed by observing an increase in a fluorescence signal.
- [74] Antibodies that block human and/or rat TIMP-1 activity can be screened in an ELISA assay that detects the decrease of TIMP-1/MMP-1 complex formation in cultures of

HepG2 cells. Antibodies that meet this criteria can then be tested in a rat liver fibrosis model to assess therapeutic efficacy and correlate this efficacy with the ability of the antibodies to block TIMP-1 inhibition of MMP-1 *in vitro*.

- [75] Antibodies that demonstrate therapeutic efficacy in the rat liver fibrosis model can then be tested for binding to and blockade of TIMP-2, -3, and -4 in an *in vitro* enzymatic assay. Blocking the minimum number of TIMPs necessary for efficacy in liver fibrosis or other TIMP-associated pathology is preferable to minimize potential side effects.

Polynucleotides encoding human TIMP-1 antibodies

- [76] The invention also provides polynucleotides encoding human TIMP-1 antibodies. These polynucleotides can be used, for example, to produce quantities of the antibodies for therapeutic or diagnostic use.
- [77] Polynucleotides that can be used to encode the VHCDR3 regions shown in SEQ ID NOS:1-43 are shown in SEQ ID NOS:226-268, respectively. Polynucleotides that can be used to encode the VLCDR3 region shown in SEQ ID NOS:44-86 are shown in SEQ ID NOS:183-225, respectively. Polynucleotides that encode heavy chains (SEQ ID NOS:140-182) and light chains (SEQ ID NOS:97-139) of human antibodies of the invention that have been isolated from the MorphoSys HuCAL[®] library are shown in SEQ ID NOS:269-311 and SEQ ID NOS:312-354, respectively.
- [78] Polynucleotides of the invention present in a host cell can be isolated free of other cellular components such as membrane components, proteins, and lipids. Polynucleotides can be made by a cell and isolated using standard nucleic acid purification techniques, or synthesized using an amplification technique, such as the polymerase chain reaction (PCR), or by using an automatic synthesizer. Methods for isolating polynucleotides are routine and are known in the art. Any such technique for obtaining a polynucleotide can be used to obtain isolated polynucleotides encoding antibodies of the invention. For example, restriction enzymes and probes can be used to

isolate polynucleotides which encode the antibodies. Isolated polynucleotides are in preparations that are free or at least 70, 80, or 90% free of other molecules.

[79] Human antibody-encoding DNA molecules of the invention can be made with standard molecular biology techniques, using mRNA as a template. Thereafter, DNA molecules can be replicated using molecular biology techniques known in the art and disclosed in manuals such as Sambrook *et al.* (1989). An amplification technique, such as PCR, can be used to obtain additional copies of the polynucleotides.

[80] Alternatively, synthetic chemistry techniques can be used to synthesize polynucleotides encoding antibodies of the invention. The degeneracy of the genetic code allows alternate nucleotide sequences to be synthesized that will encode an antibody having, for example, one of the VHCDR3, VLCDR3, light chain, or heavy chain amino acid sequences shown in SEQ ID NOS:1-43, 44-86, 97-139, or 140-182, respectively.

Expression of polynucleotides

[81] To express a polynucleotide encoding a human antibody of the invention, the polynucleotide can be inserted into an expression vector that contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods that are well known to those skilled in the art can be used to construct expression vectors containing sequences encoding human antibodies and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook *et al.* (1989) and in Ausubel *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, N.Y., 1995. See also Examples 1-3, below.

[82] A variety of expression vector/host systems can be utilized to contain and express sequences encoding a human antibody of the invention. These include, but are not limited to, microorganisms, such as bacteria transformed with recombinant

bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors, insect cell systems infected with virus expression vectors (e.g., baculovirus), plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids), or animal cell systems.

- [83] The control elements or regulatory sequences are those non-translated regions of the vector -- enhancers, promoters, 5' and 3' untranslated regions -- which interact with host cellular proteins to carry out transcription and translation. Such elements can vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, can be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the BLUESCRIPT phagemid (Stratagene, LaJolla, Calif.) or pSPORT1 plasmid (Life Technologies) and the like can be used. The baculovirus polyhedrin promoter can be used in insect cells. Promoters or enhancers derived from the genomes of plant cells (e.g., heat shock, RUBISCO, and storage protein genes) or from plant viruses (e.g., viral promoters or leader sequences) can be cloned into the vector. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are preferable. If it is necessary to generate a cell line that contains multiple copies of a nucleotide sequence encoding a human antibody, vectors based on SV40 or EBV can be used with an appropriate selectable marker.

- [84] Large scale production of human TIMP-1 antibodies can be carried out using methods such as those described in Wurm *et al.*, *Ann. N.Y. Acad. Sci.* 782, 70-78, 1996, and Kim *et al.*, *Biotechnol. Bioengineer.* 58, 73-84, 1998.

Pharmaceutical compositions

- [85] Any of the human TIMP-1 antibodies described above can be provided in a pharmaceutical composition comprising a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier preferably is non-pyrogenic. The compositions can

be administered alone or in combination with at least one other agent, such as stabilizing compound, which can be administered in any sterile, biocompatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose, and water. A variety of aqueous carriers may be employed, *e.g.*, 0.4% saline, 0.3% glycine, and the like. These solutions are sterile and generally free of particulate matter. These solutions may be sterilized by conventional, well known sterilization techniques (*e.g.*, filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, etc. The concentration of the antibody of the invention in such pharmaceutical formulation can vary widely, *i.e.*, from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected. See U.S. Patent 5,851,525. If desired, more than one type of human antibody, for example with different K_d for TIMP-1 binding or with different IC_{50} s for MMP-inhibiting activity neutralization, can be included in a pharmaceutical composition.

- [86] The compositions can be administered to a patient alone, or in combination with other agents, drugs or hormones. In addition to the active ingredients, these pharmaceutical compositions can contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations which can be used pharmaceutically. Pharmaceutical compositions of the invention can be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, parenteral, topical, sublingual, or rectal means.
- [87] After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. Such labeling would include amount, frequency, and method of administration.

Methods of decreasing MMP-inhibiting activity of human TIMP-1

- [88] The invention provides methods of decreasing an MMP-inhibiting activity of human or rat TIMP-1. Such methods can be used therapeutically, as described below, or in a research setting. Thus, the methods can be carried out in a cell-free system, in a cell culture system, or *in vivo*. *In vivo* methods of decreasing MMP-inhibiting activity of human or rat TIMP-1 are described below.
- [89] Human TIMP-1 is contacted with a human antibody that binds to the human TIMP-1, thereby decreasing the MMP-inhibiting activity of the human TIMP-1 relative to human TIMP-1 activity in the absence of the antibody. The antibody can be added directly to the cell-free system, cell culture system, or to an animal subject or patient, or can be provided by means of an expression vector encoding the antibody.

Diagnostic methods

- [90] The invention also provides diagnostic methods, with which human or rat TIMP-1 can be detected in a test preparation, including without limitation a sample of serum, lung, liver, heart, kidney, colon, a cell culture system, or a cell-free system (*e.g.*, a tissue homogenate). Such diagnostic methods can be used, for example, to diagnose disorders in which TIMP-1 is elevated. Such disorders include, but are not limited to, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis. When used for diagnosis, detection of an amount of the antibody-TIMP-1 complex in a test sample from a patient which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.
- [91] The test preparation is contacted with a human antibody of the invention, and the test preparation is then assayed for the presence of an antibody-TIMP-1 complex. If desired, the human antibody can comprise a detectable label, such as a fluorescent, radioisotopic,

chemiluminescent, or enzymatic label, such as horseradish peroxidase, alkaline phosphatase, or luciferase.

- [92] Optionally, the antibody can be bound to a solid support, which can accommodate automation of the assay. Suitable solid supports include, but are not limited to, glass or plastic slides, tissue culture plates, microtiter wells, tubes, silicon chips, or particles such as beads (including, but not limited to, latex, polystyrene, or glass beads). Any method known in the art can be used to attach the antibody to the solid support, including use of covalent and non-covalent linkages, passive absorption, or pairs of binding moieties attached to the antibody and the solid support. Binding of TIMP-1 and the antibody can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and microcentrifuge tubes.

Therapeutic methods

- [93] The invention also provides methods of ameliorating symptoms of a disorder in which TIMP-1 is elevated. These disorders include, without limitation, liver fibrosis alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, colon cancer, and scarring. *See, e.g., Inokubo et al., Am. Heart J. 141, 211-17, 2001; Ylisirnio et al., Anticancer Res. 20, 1311-16, 2000; Holten-Andersen et al., Clin. Cancer Res. 6, 4292-99, 2000; Holten-Andersen et al., Br. J. Cancer 80, 495-503, 1999; Peterson et al., Cardiovascular Res. 46, 307-15, 2000; Arthur et al., Alcoholism: Clinical and Experimental Res. 23, 840-43, 1999; Iredale et al., Hepatol. 24, 176-84, 1996.*
- [94] Human antibodies of the invention are particularly useful for treating liver fibrosis. All chronic liver diseases cause the development of fibrosis in the liver. Fibrosis is a programmed uniform wound healing response. Toxic damage or injury caused by foreign proteins cause the deposition of extracellular matrix such as collagen, fibronectin, and laminin. Liver fibrosis and cirrhosis can be caused by chronic degenerative diseases

of the liver such as viral hepatitis, alcohol hepatitis, autoimmune hepatitis, primary biliary cirrhosis, cystic fibrosis, hemochromatosis, Wilson's disease, and non-alcoholic steato-hepatitis, as well as chemical damage.

- [95] Altered degradation and synthesis of extracellular matrix (particularly collagens) play central roles in pathogenesis of liver fibrosis. In the early phases, hepatic stellate cells (HSC) are initially activated and release matrix metalloproteases with the ability to degrade the normal liver matrix. When HSC are fully activated, there is a net down-regulation of matrix degradation mediated by increased synthesis and extracellular release of tissue inhibitors of metalloprotease (TIMP)-1 and -2. The dynamic regulation of activity of metalloproteases during liver fibrosis makes them and their inhibitors targets for therapeutic intervention.
- [96] Human antibodies of the invention are also particularly useful for treating lung fibrosis. Lung airway fibrosis is a hallmark of airway remodeling in patients with chronic asthma, so human antibodies of the invention are also particularly useful for chronic asthma. Airway remodeling is a well-recognized feature in patients with chronic asthma. TIMP-1 but not TIMP-2 levels were significantly higher in untreated asthmatic subjects than in glucocorticoid-treated subjects or controls ($p < 0.0001$), and were far greater than those of MMP-1, MMP-2, MMP-3, and MMP-9 combined (Mautino *et al.*, Am J Respir Crit Care Med 1999 160:324-330). TIMP-1 mRNA and protein expression are selectively and markedly increased in a murine model of bleomycin-induced pulmonary fibrosis (Am. J. Respir. Cell Mol. Biol. 24:599-607, 2001). This specific elevation of TIMP-1 without increase in MMPs in asthma patients suggests that inhibition of TIMP-1 by an antibody can restore normal collagen degradation in the lung.
- [97] Human antibodies of the invention are also particularly useful for treating cancer. TIMP-1 protein has been found to be elevated in plasma of colon (Holten-Andersen *et al.*, Br J Cancer 1999, 80:495-503) and prostate (Jung *et al.*, Int J Cancer, 1997, 74:220-223) cancer patients, and high TIMP-1 plasma level correlates with poor clinical outcome of

colon cancer (Holten-Andersen et al., Clin Cancer Res 2000 6:4292-4299). TIMP-1 induces dose-dependent proliferation of breast tumorigenic clonal cell line and tyrosine phosphorylation (Luparello et al, Breast Cancer Res Treat, 1999, 54:235-244). Therefore, the use of antibody against TIMP-1 may block its ability to induce cancer.

- [98] Human TIMP-1 antibodies can be used to prevent or diminish scar formation, such as scar formation after surgery (particularly ophthalmic surgery) or injury (such as a burn, scrape, crush, cut or tear injury).
- [99] In one embodiment of the invention, a therapeutically effective dose of a human antibody of the invention is administered to a patient having a disorder in which TIMP-1 is elevated, such as those disorders described above. Symptoms of the disorder, including deposition of extracellular matrix, as well as loss of tissue or organ function, are thereby ameliorated.

Determination of a Therapeutically Effective Dose

- [100] The determination of a therapeutically effective dose is well within the capability of those skilled in the art. A therapeutically effective dose refers to that amount of human antibody that reduces MMP-inhibiting activity of the TIMP-1 relative to the activity which occurs in the absence of the therapeutically effective dose.
- [101] The therapeutically effective dose can be estimated initially either in cell culture assays or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model also can be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. A rat liver fibrosis model is described in Example 6.
- [102] Therapeutic efficacy and toxicity, e.g., ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population) of a human antibody, can be determined by standard pharmaceutical procedures in cell cultures or experimental

animals. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50} .

- [103] Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.
- [104] The exact dosage will be determined by the practitioner, in light of factors related to the patient who requires treatment. Dosage and administration are adjusted to provide sufficient levels of the human antibody or to maintain the desired effect. Factors that can be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on the half-life and clearance rate of the particular formulation.
- [105] Polynucleotides encoding human antibodies of the invention can be constructed and introduced into a cell either *ex vivo* or *in vivo* using well-established techniques including, but not limited to, transferrin-polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, "gene gun," and DEAE- or calcium phosphate-mediated transfection.
- [106] Effective *in vivo* dosages of an antibody are in the range of about 5 mg to about 50 mg/kg, about 50 mg to about 5 mg/kg, about 100 mg to about 500 mg/kg of patient body weight, and about 200 to about 250 mg/kg of patient body weight. For administration of polynucleotides encoding the antibodies, effective *in vivo* dosages are in the range of

about 100 ng to about 200 ng, 500 ng to about 50 mg, about 1 mg to about 2 mg, about 5 mg to about 500 mg, and about 20 mg to about 100 mg of DNA.

- [107] The mode of administration of human antibody-containing pharmaceutical compositions of the invention can be any suitable route which delivers the antibody to the host. Pharmaceutical compositions of the invention are particularly useful for parenteral administration, *i.e.*, subcutaneous, intramuscular, intravenous, or intranasal administration.
- [108] All patents, patent applications, and references cited in this disclosure are expressly incorporated herein by reference. The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples, which are provided for purposes of illustration only and are not intended to limit the scope of the invention.

EXAMPLE 1

Construction of a Human Combinatorial Antibody Library (HuCAL[®] Fab 1)

- [109] *Cloning of HuCAL[®] Fab 1.* HuCAL[®] Fab 1 is a fully synthetic, modular human antibody library in the Fab antibody fragment format. HuCAL[®] Fab 1 was assembled starting from an antibody library in the single-chain format (HuCAL[®]-scFv; Knappik *et al.*, *J. Mol. Biol.* 296, 55, 2000). HuCAL[®] Fab 1 was cloned into a phagemid expression vector pMORPH[®] 18 Fab1 (FIG. 3). This vector comprises the Fd fragment with a phoA signal sequence fused at the C-terminus to a truncated gene III protein of filamentous phage, and further comprises the light chain VL-CL with an ompA signal sequence. Both chains are under the control of the lac operon. The constant domains C_H1, C_H2, and C_H3 are synthetic genes fully compatible with the modular system of HuCAL[®] (Knappik *et al.*, 2000).
- [110] First, the V_H and V_L libraries were isolated from HuCAL[®]-scFv. V_H1 fragments were amplified by 15 PCR cycles (Pwo polymerase) with primers 5'-

GTGGTGGTTCCGATATC-3' (SEQ ID NO:380) and 5'- AGCGTCACA-CTCGGTGCGGCTTTTCGGCTGGCCAAGAACGGTTA-3' (SEQ ID NO:381). PCR-products were digested with EcoRV / DraIII and gel-purified. VL?-chains were obtained by restriction digest with EcoRV / BsiWI and gel-purified. These V? and V? libraries were cloned into pMORPH[®] 18 FabI cut with *EcoRV* / *DraIII* and *EcoRV* / *BsiWI*, respectively. After ligation and transformation in *E. coli* TG-1, library sizes of 4.14×10^8 and 1.6×10^8 , respectively, were obtained, in both cases exceeding the V? diversity of HuCAL[®]-scFv.

- [111] Similarly, the VH library was isolated from HuCAL[®]-scFv by restriction digest using *StyI* / *MunI*. This VH library was cloned into the pMORPH[®] 18-V? and V? libraries cut with *StyI* / *MunI*. After ligation and transformation in *E. coli* TG-1, a total library size of 2.09×10^{10} was obtained, with 67% correct clones (as identified by sequencing of 207 clones).
- [112] *Phagemid rescue, phage amplification and purification.* HuCAL[®] Fab was amplified in 2 x TY medium containing 34 µg/ml chloramphenicol and 1 % glucose (2 x TY-CG). After helper phage infection (VCSM13) at 37°C at an OD₆₀₀ of about 0.5, centrifugation and resuspension in 2 x TY / 34 µg/ml chloramphenicol/ 50 µg/ml kanamycin, cells were grown overnight at 30°C. Phage were PEG-precipitated from the supernatant (Ausubel *et al.*, 1998), resuspended in PBS/20% glycerol, and stored at -80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1-cells were infected with eluted phage and plated onto LB-agar supplemented with 1% of glucose and 34 µg/ml of chloramphenicol. After overnight incubation at 30°C, colonies were scraped off and adjusted to an OD₆₀₀ of 0.5. Helper phage were added as described above.

EXAMPLE 2

Solid phase panning

- [113] Wells of MaxiSorpTM microtiter plates (Nunc) were coated with rat- or human TIMP protein diluted to 50 µg/ml dissolved in PBS (2 µg/well). After blocking with 5% non-fat dried milk in PBS, 1–5 x 10¹² HuCAL[®] Fab phage purified as above were added for 1h at 20°C. After several washing steps, bound phage were eluted by pH-elution with 100 mM triethylamine and subsequent neutralization with 1M TRIS-Cl pH 7.0. See Krebs *et al.*, *J. Immunol. Meth.* 254, 67, 2001. Two to three rounds of panning were performed with phage amplification conducted between each round as described above.

EXAMPLE 3

Solution panning

- [114] Biotinylated antigen was diluted to 40 nM in PBS, 1013 HuCAL[®]-Fab 1 phage were added and incubated for 1 h at 20°C. Phage-antigen complexes were captured on Neutravidin plates (Pierce). After several washing steps, bound phages were eluted by different methods (Krebs *et al.*, 2001). Two rounds of panning were routinely performed.

EXAMPLE 4

Subcloning of selected Fab fragments for expression

- [115] The Fab-encoding inserts of the selected HuCAL[®] Fab 1 fragments were subcloned into the expression vector pMORPH[®] x7_FS (Knappik *et al.*, *J. Mol. Biol.* 296, 55, 2000) to facilitate rapid expression of soluble Fab. The DNA preparation of the selected HuCAL[®] Fab 1 clones was digested with *Xba*I / *Eco*RI, thus cutting out the Fab encoding insert (ompA-VL and phoA-Fd). Subcloning of the purified inserts into the *Xba*I / *Eco*RI cut vector pMORPH[®] x7, previously carrying a scFv insert, produces a Fab expression vector designated pMORPH[®] x9_Fab1_FS (FIG. 4). Fabs expressed in this vector carry two C-terminal tags (FLAGTM and Strep-tagII) for detection and purification.

EXAMPLE 5

Identification of TIMP-binding Fab fragments by ELISA

- [116] The wells of 384-well Maxisorp ELISA plates were coated with 20 μ l/well solutions of rat TIMP or human TIMP at a concentration of 5 μ g/ml diluted in coating buffer. Expression of individual Fab in *E. coli* TG-1 from expression vector pMORPH[®] x9_FS was induced with 0.5 mM IPTG for 12 h at 30°C. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used in an ELISA. The Fab fragment was detected after incubation with alkaline phosphatase-conjugated anti-Fab antibody (Dianova), followed by development with Attophos substrate (Roche) and measurement at Ex450 nm / Em535 nm. Values at 370 nm were read out after addition of horseradish peroxidase-conjugated anti-mouse IgG antibody and POD soluble substrate (Roche Diagnostics).

EXAMPLE 6

Expression and purification of HuCAL[®]-Fab 1 antibodies in E. coli

- [117] Expression of Fab fragments encoded by pMORPH[®] x9_FS in TG-1 cells was carried out in shaker flask cultures with 1 liter of 2xTY medium supplemented with 34 μ g/ml chloramphenicol. After induction with 0.5 mM IPTG, cells were grown at 22°C for 16 h. Periplasmic extracts of cell pellets were prepared, and Fab fragments were isolated by Strep-tactin[®] chromatography (IBA, Goettingen, Germany). The apparent molecular weights were determined by size exclusion chromatography (SEC) with calibration standards. Concentrations were determined by UV-spectrophotometry.

EXAMPLE 7

Construction of HuCAL[®] immunoglobulin expression vectors

- [118] *Heavy chain cloning.* The multiple cloning site of pcDNA3.1+ (Invitrogen) was removed (*NheI* / *ApaI*), and a stuffer compatible with the restriction sites used for HuCAL[®] design

was inserted for the ligation of the leader sequences (*NheI* / *EcoRI*), VH-domains (*EcoRI* / *BlnI*), and the immunoglobulin constant regions (*BlnI* / *ApaI*). The leader sequence (EMBL M83133) was equipped with a Kozak sequence (Kozak, 1987). The constant regions of human IgG₁ (PIR J00228), IgG₄ (EMBL K01316), and serum IgA₁ (EMBL J00220) were dissected into overlapping oligonucleotides with lengths of about 70 bases. Silent mutations were introduced to remove restriction sites non-compatible with the HuCAL[®] design. The oligonucleotides were spliced by overlap extension-PCR.

[119] *Light chain cloning.* The multiple cloning site of pcDNA3.1/Zeo⁺ (Invitrogen) was replaced by two different stuffers. The λ -stuffer provided restriction sites for insertion of a λ -leader (*NheI* / *EcoRV*), HuCAL[®]-scFv V λ -domains (*EcoRV* / *BsiWI*), and the λ -chain constant region (*BsiWI* / *ApaI*). The corresponding restriction sites in the λ -stuffer were *NheI* / *EcoRV* (λ -leader), *EcoRV* / *HpaI* (V λ - domains), and *HpaI* / *ApaI* (λ -chain constant region). The λ -leader (EMBL Z00022) as well as the λ -leader (EMBL L27692) were both equipped with Kozak sequences. The constant regions of the human λ - (EMBL J00241) and λ -chain (EMBL M18645) were assembled by overlap extension-PCR as described above.

[120] *Generation of IgG-expressing CHO-cells.* CHO-K1 cells were co-transfected with an equimolar mixture of IgG heavy and light chain expression vectors. Double-resistant transfectants were selected with 600 μ g/ml G418 and 300 μ g/ml Zeocin (Invitrogen) followed by limiting dilution. The supernatant of single clones was assessed for IgG expression by capture-ELISA (see below). Positive clones were expanded in RPMI-1640 medium supplemented with 10% ultra-low IgG-FCS (Life Technologies). After adjusting the pH of the supernatant to 8.0 and sterile filtration, the solution was subjected to standard protein A column chromatography (Poros 20 A, PE Biosystems).

EXAMPLE 8

Design of the CDR3 libraries

- [121] *V?* positions 1 and 2. The original HuCAL[®] master genes were constructed with their authentic N-termini: V?11: QS (CAGAGC), V?12: QS (CAGAGC), and V?13: SY (AGCTAT). Sequences containing these amino acids are shown in WO 97/08320. During HuCAL[®] library construction, the first two amino acids were changed to DI to facilitate library cloning (*EcoRI* site). All HuCAL[®] libraries contain V?1 genes with the *EcoRV* site GATATC (DI) at the 5'-end. All HuCAL[®] kappa genes (master genes and all genes in the library) contain DI at the 5'-end.
- [122] *VH position 1*. The original HuCAL[®] master genes were constructed with their authentic N-termini: VH1A, VH1B, VH2, VH4, and VH6 with Q (=CAG) as the first amino acid and VH3 and VH5 with E (=GAA) as the first amino acid. Sequences containing these amino acids are shown in WO 97/08320. In the HuCAL[®] Fab 1 library, all VH chains contain Q (=CAG) at the first position.
- [123] *V?1/V?3 position 85*. Because of the cassette mutagenesis procedure used to introduce the CDR3 library (Knappik *et al.*, *J. Mol. Biol.* 296, 57-86, 2000), position 85 of V?1 and V?3 can be either T or V. Thus, during HuCAL[®] scFv 1 library construction, position 85 of V?1 and V?3 was varied as follows: V?1 original, 85T (codon ACC); V?1 library, 85T or 85V (TRIM codons ACT or GTT); V?3 original, 85V (codon GTG); V?3 library, 85T or 85V (TRIM codons ACT or GTT); the same applies to HuCAL[®] Fab1.
- [124] *CDR3 design*. All CDR3 residues which were kept constant are indicated in FIG. 1.
- [125] *CDR3 length*. The designed CDR3 length distribution is as follows. Residues which were varied are shown in brackets (x) in FIG. 1. V kappa CDR3, 8 amino acid residues (position 89 to 96) (occasionally 7 residues), with Q90 fixed; V lambda CDR3, 8 to 10 amino acid residues (position 89 to 96) (occasionally 7-10 residues), with Q89, S90, and

D92 fixed; and VH CDR3, 5 to 28 amino acid residues (position 95 to 102) (occasionally 4-28), with D101 fixed.

EXAMPLE 9

Chronic carbon tetrachloride-induced liver fibrosis

- [126] Sprague Dawley rats (200-220 g) are used in an *in vivo* model of liver fibrosis. To maximally induce microsomal metabolism of carbon tetrachloride metabolism, animals receive 1 g/l isoniazid with their drinking water starting one week before the administration of carbon tetrachloride. Carbon tetrachloride (1:1 in mineral oil) is administered orally every fifth day at a dose of 0.2 ml/100 g body weight. A human TIMP-1 antibody is administered intravenously, either once or repeatedly, during the period of carbon tetrachloride treatment. Necropsy is performed after 5-7 weeks of treatment. McLean *et al.*, *Br. J. Exp. Pathol.* 50, 502-06, 1969.
- [127] Transverse cylinders of liver tissue are cut from the right liver lobe, fixed in formaldehyde, and embedded in paraffin. The amount of fibrosis in the liver is indicated by the picrosirius red-stained fibrotic areas. Picrosirius-positive areas are determined in several centrilobular fields in each section. Parameters of color detection are standardized and kept constant throughout the experiment. The field are selected using a standardized grid which covers an area of 31 mm². A Leica Quantimed 500 MC system is used for morphometry.

EXAMPLE 10

Hydroxyproline determination

- [128] The method of Prockop & Udenfried, *Anal. Biochem.* 1, 228-39, 1960, can be used to determine hydroxyproline in liver tissues, with the following modifications. Liver specimens of 60-90 mg wet weight are dried and hydrolyzed in 6 N HCl at 100 °C for 17 h. The hydrolyzed material is dried and reconstituted in 5 ml of deionized water. Two

hundred microliters of this hydrolysate are mixed with 200 ml of ethanol and 200 ml chloramin T solution (0.7 % in citrate buffer [5.7 g sodium acetate, 3.75 g trisodium citrate, 0.55 g citric acid, 38.5 ml ethanol, made up to 100 ml with water]) and allowed to oxidize for 20 min at room temperature. Four hundred microliters of Ehrlich's reagent (12 g p-dimethylaminobenzaldehyde in 40 ml ethanol and 2.7 ml H₂SO₄) are added. After incubation for 3 h at 35 °C, absorbance at 573 nm is measured.

EXAMPLE 11

Affinity determination by surface plasmon resonance measurements (BIAcore™)

- [129] For affinity determination, monomeric fractions of affinity and SEC purified Fab fragments or purified IgG1 molecules were used. All experiments were conducted in HBS buffer at a flow rate of 20 µl/min at 25°C on a BIAcore™ instrument. Antigens in 100 mM sodium acetate pH 5.0 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 3-4 µl of 5 µg/ml TIMP-1 typically resulted in 500 resonance units for kinetic measurements. All sensograms were fitted globally using BIA evaluation software. For monovalent Fab fragments a monovalent fit (Langmuir binding) and for IgGs a bivalent fit was applied.

EXAMPLE 12

IC₅₀ determination in human TIMP-1/human MMP-1 and rat TIMP-1/rat MMP-13 assay

- [130] Purified Fab fragments or IgGs were used for IC₅₀ determination. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), MMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), and peptide substrate (final conc. 50 µM) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em430 nm was measured.

[131] The following controls were included in the assay and used as reference values for IC_{50} determination:

A: MMP + substrate: this value was defined as 100% MMP activity in absence of antibody and TIMP.

B: MMP + TIMP + substrate: this value was defined as maximum inhibition achieved in the assay and calculated as a % of total MMP activity.

[132] To define the concentration of antibody that resulted in 50% reversal of inhibition (IC_{50}), the following procedure was used:

- The value for 50% reversal of inhibition (expressed as % activity MMP) was calculated as: $Y = [(A - B)/2] + B$.
- MMP activity was plotted against concentration of antibody in the assay.
- The concentration of antibody that results in 50% reversal of inhibition (Y) was read on the x-axis and defined as IC_{50} .
- Error bars in the graphs were derived from triplicate wells in one assay.
- Standard deviations for IC_{50} values were calculated from 3 independent assays.

EXAMPLE 13

Affinity maturation of selected Fab by stepwise exchange of CDR cassettes

[133] To increase affinity and biological activity of selected antibody fragments, CDR regions were optimized by cassette mutagenesis using trinucleotide directed mutagenesis (Virnekås *et al.*, 1994). Fab fragments in expression vector pMORPH[®] x9 were cloned into phagemid vector pMORPH[®] _18 using *EcoRI* / *XbaI* restriction sites. CDR cassettes containing several diversified positions were synthesized and cloned into Fab fragments in pMORPH[®] _18 using unique restriction sites (Knappik *et al.*, 2000). Affinity

maturation libraries were generated by transformation into *E. coli* TOP10F, and phage were prepared as described above. Phage displaying Fab fragments with improved affinity were selected by 2-3 rounds solution panning using stringent washing conditions (e.g., competition with 1 μ M non-biotinylated antigen or washing for up to 48 h with frequent buffer exchange) and limited amounts of antigen (0.04 – 4 nM). Seventeen human TIMP-1 antibodies were tested for affinity to human TIMP-1 (with some tested for affinity to rat TIMP-1) using a BIAcoreTM assay. The K_d of these antibodies for human TIMP-1 and rat TIMP-1 are shown in Table 1.

Table 1. Overview of species cross-reactive Fab

Fab	Monovalent K _D human TIMP-1	Monovalent K _D rat TIMP-1	IC ₅₀ in human protease assay	IC ₅₀ in rat protease assay
MS-BW-25	25 +/- 16 nM*	4517 +/- 2400 nM	115 +/- 15 nM	> 300 nM
MS-BW-27	~74 nM	~ 3200 nM	Non blocking	
MS-BW-21	520 +/- 20 nM	36 +/- 2 nM	> 300 nM	67 +/- 5 nM
MS-BW-38	~3 nM	~353 nM	~11 nM	> 300 nM
MS-BW-39	~7500 nM	~108 nM	> 100 nM	> 100 nM

* In cases where standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 14

Screening for Fab with improved off-rates by koff ranking using surface plasmon resonance

- [134] Phage eluted after solution panning were used to infect *E. coli* TG-1 and plated on agar plates containing 34 µg/ml chloramphenicol. Clones were picked into 96 well plates and used to produce Fab fragments. On the same plate, parental clones were inoculated as controls. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used for koff ranking in BIAcore™.
- [135] All measurements were conducted in HBS buffer at a flow rate of 20 µl/min at 25°C on a BIAcore™ instrument. Antigens in 100 mM sodium acetate pH 4.5 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 10 µl of 25 µg/ml TIMP-1 typically resulted in 5000 resonance units for koff ranking. All sensograms were fitted using BIA evaluation software. Clones with improved off rate were selected by comparison to parental clones.

EXAMPLE 15

Generation of species cross-reactive antibodies

- [136] To maximize the likelihood of obtaining blocking antibodies that are cross-reactive between human and rat TIMP-1, alternating pannings were carried out on rat and human protein. Additionally, all antibodies selected by pannings on solely the human or rat TIMP-1 protein were analyzed for cross-reactivity in order to check for cross-reactive antibodies that might be selected by chance. Antibodies selected from these pannings were analyzed for cross-reactivity in ELISA using crude *E. coli* extracts. Cross-reactive antibodies in this assay were subjected to expression in 1-liter scale followed by purification. Purified antibodies were tested for cross-reactivity in BIAcore™ and protease assays (Table 1).

- [137] As shown in Table 1, a total of five different Fab cross-reactive with human and rat TIMP-1 were generated. BIAcore™ measurements revealed that although these antibodies clearly bind to human and rat TIMP-1, affinities for both species differ by at least a factor of 50. An antibody used for human therapy or in an animal model should have an affinity to the target protein in the low nanomolar, preferably in the sub-nanomolar range. As none of the above-described antibodies had affinities in this range for both species, these antibodies were not considered useful for further experiments or development.

EXAMPLE 16

Generation of blocking antibodies against human TIMP-1

- [138] To generate blocking antibodies against human TIMP-1, the HuCAL®-Fab 1 library was used for antibody selection (AutoPan®) on purified TIMP-1 protein followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen®). Purified Fab proteins were subjected to further characterization in ELISA, TIMP-1/MMP-1 assay and BIAcore™. A total of 6100 clones were analyzed in AutoScreen®, 670 of them showed binding to human TIMP-1. Sequence analysis revealed that in total seven unique antibody clones had been selected (Table 2). For these seven Fab clones, the affinities measured in BIAcore™ were in the range of 10 – 180 nM (Table 4). When tested in the human protease assay, five of them were able to block the interaction between human TIMP-1 and MMP-1. The concentration of monovalent Fab needed to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% (IC₅₀) was in the range of 11 - 100 nM (Table 2). The most active Fab clones are MS-BW-3 (K_d 13 nM; IC₅₀ 11 nM) and MS-BW-28 (K_d 10 nM; IC₅₀ 22 nM).
- [139] A striking feature of antibodies selected against human TIMP-1 is that they all exhibit the combination VH312 and a relatively short VH-CDR3 region, predominantly four amino acids (see Table 2). The HCDR3 cassettes assembled for the HuCAL®-Fab 1 library

were designed to achieve a length distribution ranging from 5 to 28 amino acid residues. A four amino acid HCDR3 can occur in the library due to TRIM deletion, but is considered a very rare event. Another remarkable feature was the high degree of sequence homology among the selected LCDR3 sequences.

Table 2. Overview of anti-human TIMP-1 Fab

Fab	Framework + CDR 3 sequence				Monovalent K _D to human TIMP-1	IC ₅₀ in human protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-1	H3	FMDI, SEQ ID NO:1	?2	QSYDYQQFT, SEQ ID NO:44	65+/-13 nM*	>100 nM
MS-BW-2	H3	GFDY, SEQ ID NO:2	?2	QSYDFKTYL, SEQ ID NO:45	180+/-28 nM	>100 nM
MS-BW-3	H3	FLDI, SEQ ID NO:3	?2	QSYDFLRFS, SEQ ID NO:46	13+/-2 nM	11+/-2nM
MS-BW-25	H3	TFPIDADS, SEQ ID NO:4	?2	QSYDFINVI, SEQ ID NO:47	25+/-16nM	115+/-15 nM
MS-BW-26	H3	GHVDY, SEQ ID NO:5	?2	QSYDFVREM, SEQ ID NO:48	~100 nM	non blocking
MS-BW-27	H3	YWRGLSFDI, SEQ ID NO:6	?2	QSYDFYKFN, SEQ ID NO:49	~74	non blocking
MS-BW-28	H3	FFDY, SEQ ID NO:7	?2	QSYDFRRFS, SEQ ID NO:50	10+/-1 nM	22+/-2nM

* In cases where standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 17

Increasing the affinity of selected anti-human TIMP-1 antibodies

- [140] In order to increase the affinity of monovalent anti-human TIMP-1 Fab fragments to the sub-nanomolar range, a step-wise affinity maturation approach was applied, by optimizing CDR sequences and keeping framework regions constant.

Affinity maturation by light chain cloning

- [141] The CDR3 sequences of the two antibody fragments with highest affinity (MS-BW-3 and MS-BW-28) had the remarkable feature of an unusually short four amino acid HCDR3 sequence. Furthermore, each Fab had a very similar LCDR3 sequence. This indicates that MS-BW-3 and MS-BW-28 bind to the same epitope and that this epitope might tolerate only a very small subset of CDR3 sequences. As a four amino acid HCDR3 is a very rare event in the library, it can be anticipated that in the initial library not all possible combinations of the short HCDR3 and the preferred LCDR3 are present. Therefore, it was considered that another combination of the selected HCDR3 and LCDR3 sequences might increase the affinity. For this approach, the heavy chain of MS-BW-3 and MS-BW-28 were paired with the light chains of MS-BW-1, -2, -3, -25, -26, -27, and -28 by cloning.
- [142] The resulting constructs were transformed into *E. coli* and expressions/purifications in 1-liter scale were performed. Of the 12 new constructs, 10 resulted in functional Fab molecules. These were analyzed in BIAcore™ and human protease assay as summarized in Table 3. The best antibody named MS-BW-44 had a monovalent affinity of 2 nM and an IC50 of 4 nM (FIG. 7) and was thus improved by a factor of 6.5 (K_d) or 2.75 (IC_{50}).

Table 3. Overview of Fab derived from light chain cloning

Fab	Framework + CDR 3 sequence				Monovalent K_D to human TIMP-1	IC ₅₀ * in human protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-40	H3	FLDI, SEQ ID NO:3	?2	QSYDYQQFT, SEQ ID NO:44	~49 nM	> 100 nM
MS-BW-41	H3	FLDI, SEQ ID NO:3	?2	QSYDFKTYL, SEQ ID NO:45	~6 nM	29+/-6nM
MS-BW-43	H3	FLDI, SEQ ID NO:3	?2	QSYDFINVI, SEQ ID NO:47	~65 nM	> 100 nM
MS-BW-44	H3	FLDI, SEQ ID NO:3	?2	QSYDFVRFM, SEQ ID NO:48	2 +/- 0.4 nM*	4+/-1 nM
MS-BW-45	H3	FLDI, SEQ ID NO:3	?2	QSYDFYKFN, SEQ ID NO:49	8 +/- 5 nM	9+/-3 nM
MS-BW-46	H3	FLDI, SEQ ID NO:3	?2	QSYDFRRFS, SEQ ID NO:50	6 +/- 3 nM	4+/-0.5 nM
MS-BW-47	H3	FFDY, SEQ ID NO:7	?2	QSYDYQQFT, SEQ ID NO:44	~152 nM	> 100 nM
MS-BW-49	H3	FFDY, SEQ ID NO:7	?2	QSYDFKTYL, SEQ ID NO:45	~21 nM	> 100 nM
MS-BW-51	H3	FFDY, SEQ ID NO:7	?2	QSYDFINVI, SEQ ID NO:47	~7 nM	7+/-1 nM
MS-BW-52	H3	FFDY, SEQ ID NO:7	?2	QSYDFVRFM, SEQ ID NO:48	~11 nM	9+/-1 nM

* In cases where standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

Affinity maturation by optimizing HCDR1 and HCDR2

[143] In the HuCAL[®]-Fab 1 library, only the CDRs HCDR3 and LCDR3 are diversified to a high extent. Although it is known from crystallographic studies that amino acids from these two CDRs make most of the antibody antigen contacts, the residual four CDRs are also important for antigen binding. However, their contribution to the binding energy can vary from antibody to antibody. In the HuCAL[®]-Fab 1 library those CDRs exhibit only a limited variability due to the presence of the different master frameworks (Knappik *et al.*, 2000). In order to improve the affinity of the selected antibodies, an affinity maturation approach by randomizing HCDR1 and HCDR2 was applied. For this approach two affinity maturation libraries based on MS-BW-44 cloned into phage display vector pMORPH[®] 18 were created. In library 1, only HCDR2 of MS-BW-44 was diversified using "TRIM technology" as described in Virnekäs *et al.*, *Nucl. Acids. Res.* 22, 5600-07, 1994; Knappik *et al.*, *J. Mol. Biol.* 296, 57-86, 2000. In library 2, both HCDR1 and HCDR2 were diversified using the TRIM technology. In both cases, phage antibody libraries comprising 1×10^8 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan[®] procedure. In order to select antibodies having an increased affinity to human TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied. Antibody off rates were ranked by BIAcore[™] using crude *E. coli* extracts of selected antibodies. Clones with slower off rate than parental clone MS-BW-44 were subjected to 1-liter scale expression and purification. Purified Fab were analyzed in BIAcore[™] and human protease assay (Table 4).

Table 4. Comparison of Fab derived from HCDR1 and HCDR2 optimization with parental clone MS-BW-44

Fab	Monovalent K_D to human TIMP-1	IC_{50} in human protease assay*
MS-BW-44	2 +/- 0.4 nM	2 +/- 0.5 nM
MS-BW-44-2	0.5 +/- 0.2 nM	0.4 +/- 0.3 nM
MS-BW-44-6	0.6 +/- 0.2 nM	0.2 +/- 0.1 nM

* IC_{50} values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1 (0.4 nM each).

[144] Clone MS-BW-44-2 was derived from library 1 thus having a modified HCDR2 cassette. Its affinity measured by BIAcore™ was 0.5 nM. Clone MS-BW-44-6 was derived from library 2 having a modified HCDR 1 and HCDR 2 cassette and the affinity measured by BIAcore™ was 0.6 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8.

Table 8: Overview and sequence comparison of affinity matured Fab fragments against human TIMP-1. Sequence changes compared to parental Fab fragments (bold) are italicized

Clone MS-BW-	VH			VL				Monov. K _D to human TIMP-1 (nM)	IC ₅₀ in human protease assay (nM)
	Frame-work	HCDR1 sequence (SEQ ID NO:)	HCDR2 sequence (SEQ ID NO:)	HCDR3 sequence (SEQ ID NO:)	Framework	LCDR1 sequence (SEQ ID NO:)	LCDR2 sequence (SEQ ID NO:)	LCDR3 sequence (SEQ ID NO:)	
3	VH3	GFTSSYAMS (355)	AISGGG STYYADSVKG (357)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDFLAFS (47)	13 +/- 2
44	VH3	GFTSSYAMS (355)	AISGGG STYYADSVKG (357)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDFVREM (48)	2 +/- 0.4
44-6	VH3	GFTSSYAMS (355)	VISGMS NTYYADSVKG (358)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDFVREM (48)	0.6 +/- 0.2
44-2	VH3	GFTSSYAMS (355)	GISGMS VLIFYADSVKG (359)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDFVREM (48)	0.5 +/- 0.2
44-2-4	VH3	GFTSSYAMS (355)	GISGMS VLIFYADSVKG (359)	GLMDY (360)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDFVREM (48)	0.2 +/- 0.02
44-2-15	VH3	GFTSSYAMS (355)	GISGMS VLIFYADSVKG (359)	WFDH (361)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDFVREM (48)	0.3 +/- 0.1
44-2-16	VH3	GFTSSYAMS (355)	GISGMS VLIFYADSVKG (359)	WFDV (362)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDFVREM (48)	0.5 +/- 0.2
44-6-1	VH3	GFTSSYAMS (355)	VISGMS NTYYADSVKG (358)	FLDI (3)	VL2	TGTSSDVGGYNYVS (363)	DVSNRPS (364)	QSYDFVREM (48)	0.2 +/- 0.1

* IC₅₀ values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1; IC₅₀ of MS-BW-44 is 2 nM under these conditions

- [145] When initially analyzed in the human TIMP-1/MMP-1 assay, it was not possible to distinguish a Fab with a sub-nanomolar affinity from a Fab with 1 nM affinity, most likely because the concentration of Fab required to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% was below the concentration of total TIMP-1 in the assay. When a modified assay was used with concentrations of TIMP-1 and MMP-1 decreased from 1.2 nM to 0.4 nM, it was possible to distinguish a 2 nM Fab from a sub-nanomolar Fab (Table 4, FIG. 8). Using this modified protease assay, MS-BW-44-2 and MS-BW-44-6 had IC_{50} values of 0.4 nM and 0.2 nM respectively. Parental clone MS-BW-44 had an IC_{50} of 2 nM under these conditions. Thus, by this affinity maturation approach, an affinity gain of a factor of 5 (K_d) or 5-10 (IC_{50}) was achieved.

Affinity maturation by optimizing HCDR3

- [146] As mentioned above, amino acid residues in HCDR3 and LCDR3 are considered the most important for antigen binding. Taking into account that a four amino acid HCDR3 was not planned in the design of HuCAL[®]-Fab 1 and thus only occurs as a rare case due to a TRIM deletion, probably not all possible combinations of the four amino acids in HCDR3 were represented in the original HuCAL[®]-Fab 1 library. Therefore, an affinity maturation library was constructed with four and five amino acid HCDR3 maturation cassettes inserted into Fab derived from the previous maturation cycle (among them MS-BW-44-2 and MS-BW-44-6). The obtained affinity maturation library had a diversity of 1×10^8 clones, therefore theoretically covering all possible four and five amino acid HCDR3 variations. Applying very stringent panning conditions, the best antibody identified, MS-BW-44-2-4, had an affinity measured by BIAcore[™] of 0.2 nM and an IC_{50} in human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8. The improvement factor gained by this affinity maturation approach is 2.5 with respect to the affinity and 2 with respect to the IC_{50} .

Affinity maturation by optimizing LCDR3

- [147] As an alternative approach, a maturation strategy was used to further optimize the light chain CDR3 sequence. This was due to the fact that in the first maturation cycle where light chain exchange cloning between selected antibodies was applied, only a very limited subset of sequence variation had been exploited. Therefore, a maturation library was constructed in which, using TRIM technology, a diversified LCDR3 cassette was inserted into Fab derived from HCDR1 and HCDR2 optimization (among them MS-BW-44-2 and MS-BW-44-6). The best Fab identified with this maturation strategy was MS-BW-44-6-1 with an affinity measured by BIAcore™ of 0.15 nM and an IC₅₀ in a human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibody and its parental clones is shown in Table 8. The improvement factor gained by this maturation approach is 4 with respect to affinity. A further improvement of the IC₅₀ in the protease assay could not be measured due to limitations in the assay.
- [148] As a result of a step-wise affinity maturation approach using four different maturation strategies, the monovalent affinity of an anti-human TIMP-1 specific Fab fragment was improved by a factor of 87 and its activity in human TIMP-1/MMP-1 assay by a factor of 55. The decision for defining the best Fab fragment has been made on the basis of K_d measurements using BIAcore™, as this method proved to be reliable for ranking antibodies with sub-nanomolar affinities, whereas the sensitivity of the human TIMP-1/MMP-1 assay was considered not suitable to rank activity of the best Fabs in the sub-nanomolar range with respect to each other.
- [149] The best Fab MS-BW-44-6-1 has an affinity measured by BIAcore™ of 0.15 nM and an IC₅₀ in human TIMP-1/MMP-1 assay of 0.2 nM. Compared to its parental clone, MS-BW-3, it has optimized LCDR3, HCDR1 and HCDR2 sequences.

EXAMPLE 18

Cross reactivity of selected anti-human TIMP-1 Fab with TIMP-2, TIMP-3, and TIMP-4

- [150] TIMP-1 belongs to a family of closely related protease inhibitors all binding to various members of the MMP family of proteases. To date there are four human TIMP proteins described. To investigate potential cross-reactivity of antibody fragments selected against human TIMP-1 with other members of the human TIMP family, an ELISA was performed in which binding of antibody fragments to immobilized purified human TIMP-1, -2, -3 or -4 was analyzed (FIG. 10). Antibody fragments binding to immobilized human TIMP-1 showed no binding to human TIMP-2, -3, -4 above background level when compared to unrelated control protein BSA.

EXAMPLE 19

Generation of blocking antibodies against rat TIMP-1

- [151] To generate blocking antibodies against rat TIMP-1, the HuCAL[®]-Fab 1 library was used for antibody selection (AutoPan[®]) on immobilized rat TIMP-1 followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen[®]). Purified Fab proteins were subjected to further characterization in ELISA, protease assays, and BIAcore[™]. Of the 8,450 selected clones were analyzed in AutoScreen[®], 750 of them showed binding to rat TIMP-1. Sequence analysis revealed that in total 36 unique Fab clones specific for rat TIMP-1 were enriched during selection (Table 7). Their affinities were measured by BIAcore[™] and were found to be in the range of 9 – 1000 nM (Table 7). When tested in the rat protease assay, all but one of them were able to block the interaction between rat TIMP-1 and rat MMP-13 (Table 7). The concentration of monovalent Fab needed to reverse the inhibitory effect of rat TIMP-1 on rat MMP-13 activity by 50% (IC₅₀) was in the range of 7 - 300 nM. The most active Fab

clones are MS-BW-14 (K_d 10 nM; IC_{50} 14 nM), MS-BW-17 (K_d 13 nM; IC_{50} 11 nM), and MS-BW-54 (K_d 9 nM; IC_{50} 7 nM).

Table 7. Overview of anti-rat TIMP-1 Fab

Fab	Framework + CDR 3 sequence				Monovalent K _D to rat TIMP-1	IC ₅₀ * in rat protease assay
	VH	HCDR3	VL	LCDR3		
MS-BW-5	H1A	GLYWA VYPYDF, SEQ ID NO:8	?1	QSRDFNRGP, SEQ ID NO:51	~210 nM	non blocking
MS-BW-6	H3	LDTYYPDLFY, SEQ ID NO:9	?1	QSYDQQRKW, SEQ ID NO:52	~68 nM	~100 nM
MS-BW-7	H1A	TYYYFDS, SEQ ID NO:10	?3	QQLYGTVS, SEQ ID NO:53	~168 nM	> 300 nM
MS-BW-9	H3	YMA YMAEIDV, SEQ ID NO:11	?1	QSYDGFKTH, SEQ ID NO:54	~256 nM	> 300 nM
MS-BW-10	H1B	LVGIVGYKPDLLYFDV, SEQ ID NO:12	?3	QSYDYSLL, SEQ ID NO:55	~200 nM	~30 nM
MS-BW-11	H3	YGAYFGLDY, SEQ ID NO:13	?3	QSYDFNFH, SEQ ID NO:56	~200 nM	>300 nM
MS-BW-12	H6	GYADISFDY, SEQ ID NO:14	?2	QSYDMIARYP, SEQ ID NO:57	~419 nM	>300 nM
MS-BW-13	H3	YYLLLDY, SEQ ID NO:15	?3	QSWDJHPFDV, SEQ ID NO:58	~939 nM	not tested
MS-BW-14	H1A	WSDQSYHYWHYPYFDV, SEQ ID NO:16	?1	QSWDLEPY, SEQ ID NO:59	10 +/- 5 nM	14 +/- 3 nM
MS-BW-15	H3	LIGYFDL, SEQ ID NO:17	?2	QSYDVLDS, SEQ ID NO:60	~80 nM	~200 nM
MS-BW-17	H5	LTNYFDSIYYDH, SEQ ID NO:18	?2	QSYDPSHPSK, SEQ ID NO:61	13 +/- 3 nM	11 +/- 3 nM
MS-BW-18	H5	LVGGGYDLMFDS, SEQ ID NO:19	?2	QSYDDMQF, SEQ ID NO:62	~153 nM	> 300 nM
MS-BW-19	H5	YVITYGYDDYHFDY, SEQ ID NO:20	?2	QSWDINHAI, SEQ ID NO:63	~187 nM	> 300 nM
MS-BW-20	H1A	SGYLDY, SEQ ID NO:21	?2	QSYDYDYDG, SEQ ID NO:64	~70 nM	> 300 nM

MS-BW-21	H1A	YIGYTNVMDIRPGYFLDY, SEQ ID NO:22	?3	QQANDEPI, SEQ ID NO:65	36 +/- 2 nM	67 +/- 5 nM
MS-BW-22	H5	FRAYGDDDFYFDV, SEQ ID NO:23	?2	QSWDNLKMPV, SEQ ID NO:66	35 nM	65 +/- 11 nM
MS-BW-23	H1B	JMWSDYGQLVKGGDI, SEQ ID NO:24	?2	QSYDVFPINR, SEQ ID NO:67	~207 nM	> 300 nM
MS-BW-24	H5	YYVTDATAYFDY, SEQ ID NO:25	?2	QSDLYFP, SEQ ID NO:68	23 nM	20 +/- 1 nM
MS-BW-29	H5	HDFDGSIFMDF, SEQ ID NO:26	?2	QSYDVTPR, SEQ ID NO:69	~214 nM	> 100 nM
MS-BW-30	H5	YAGHQYEFFDF, SEQ ID NO:27	?3	QSRDPVGF, SEQ ID NO:70	~36 nM	> 100 nM
MS-BW-31	H5	LYADADIYFDY, SEQ ID NO:28	?2	QSYDLSR, SEQ ID NO:71	~13 +/- 9 nM	> 100 nM
MS-BW-32	H1A	TKYVGSEDV, SEQ ID NO:29	?2	QSYDFSHYFF, SEQ ID NO:72	~92 nM	> 100 nM
MS-BW-36	H5	YRYPHMDF, SEQ ID NO:30	?3	QSYDLRYSH, SEQ ID NO:73	~42 nM	~75 nM
MS-BW-37	H5	LFAGLELYFDY, SEQ ID NO:31	?2	QSYDLRNR, SEQ ID NO:74	10 +/- 9 nM	> 100 nM
MS-BW-38	H3	GGFFNMDY, SEQ ID NO:32	?2	QSYDFTYGS, SEQ ID NO:75	~353 nM	> 300 nM
MS-BW-39	H1A	OYIPYHLFDY, SEQ ID NO:33	?3	QQFNDSPY, SEQ ID NO:76	~108 nM	> 100 nM
MS-BW-54	H5	YYGFEDLLFDN, SEQ ID NO:34	?2	QSYDISGYP, SEQ ID NO:77	9 +/- 1 nM	7 nM
MS-BW-55	H1B	ITYIGYDF, SEQ ID NO:35	?2	QSRDLYYVYY, SEQ ID NO:78	~23 nM	~ 100 nM
MS-BW-56	H1A	QEWYMDY, SEQ ID NO:36	?3	QSYDRSMW, SEQ ID NO:79	~170 nM	> 100 nM
MS-BW-57	H5	LYPEDLYFDY, SEQ ID NO:37	?2	QSWDVQTDK, SEQ ID NO:80	~39 nM	~60 nM
MS-BW-58	H6	WMTPPGHYGYTTFDV, SEQ ID NO:38	?3	QSWDPHY, SEQ ID NO:81	~138 nM	not tested
MS-BW-59	H5	LRVHDYAMYFDL, SEQ ID NO:39	?2	QSYDIMPER, SEQ ID NO:82	~15 nM	30 +/- 5 nM

MS-BW-60	H5	FVSYNGSVPYFDY, SEQ ID NO:40	? 2	QSMDFRLMH, SEQ ID NO:83	~30 nM	> 100 nM
MS-BW-61	H5	IIGDYVIFFDV, SEQ ID NO:41	? 2	QSFDMIHPY, SEQ ID NO:84	~51 nM	> 100 nM
MS-BW-62	H5	LFTYPFLYFDV, SEQ ID NO:42	? 2	QSDFPVM, SEQ ID NO:85	~36 nM	19 +/- 2
MS-BW-63	H5	ILTGHVLLFDY, SEQ ID NO:43	? 2	QSDNPYL, SEQ ID NO:86	~14 nM	20 +/- 1nM

* In cases where standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 20

Increasing the affinity of selected anti-rat TIMP-1 antibodies

- [152] Affinity maturation was applied to increase the affinity of monovalent anti-rat TIMP-1 Fab fragments to the sub-nanomolar range. No clear sequence homology could be identified among the light chain CDR3 sequences of the selected antibody fragments, indicating that an optimal light chain CDR3 sequence was probably not present or had not been selected from the original HuCAL[®]-Fab 1 library. We therefore started with modification of LCDR3 to increase the affinity of Fabs.
- [153] Two affinity maturation libraries based on MS-BW-14, -17, and -54 cloned into phage display vector pMORPH[®] 18 were created. In library 1, only LCDR3 was diversified using TRIM technology, as described in Virnekäs *et al.*, *Nucl. Acids. Res.* 22, 5600-07, 1994; Knappik *et al.*, *J. Mol. Biol.* 296, 57-86, 2000. In library 2, LCDR1, LCDR2, and LCDR3 were diversified simultaneously using the TRIM technology, while the connecting framework regions were kept constant. In both cases, phage antibody libraries comprising 3×10^8 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan[®] procedure. To select antibodies having an increased affinity to rat TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied.
- [154] Antibody-off-rates were ranked by BIAcore[™] using crude *E. coli* extracts. Clones with slower off rate than parental clones MS-BW-14, -17, or -54 were subjected to expression and purification in 1-liter scale. Purified Fab were analyzed in BIAcore[™] and rat protease assays (Table 6). MS-BW-17-1 (K_d 0.8 nM, IC_{50} 1.6 nM), MS-BW-17-2 (K_d 1.3 nM, IC_{50} 1.1 nM), and MS-BW-17-3 (K_d 1.9 nM, IC_{50} 3 nM) were derived from affinity maturation library 1 having an optimized LCDR3 sequence, whereas MS-BW-

54-1 (K_d 2 nM, IC_{50} 3 nM) was derived from affinity maturation library 2 having an optimized LCDR1, -2, and -3 sequence (Table 9).

Table 9. Overview and sequence comparison of affinity matured Fab fragments against rat TIMP-1. Sequence changes compared to parental Fab fragments (bold) are italicized.

Clone (MS- BW-)	VH				VL				Monov. K _D to rat TIMP-1 (nM)	IC ₅₀ in rat protease assay (nM)
	Frame- work	HCDR1 sequence (SEQ ID NO:)	HCDR2 sequence (SEQ ID NO:)	HCDR3 sequence (SEQ ID NO:)	Frame- work	LCDR1 sequence (SEQ ID NO:)	LCDR2 sequence (SEQ ID NO:)	LCDR3 sequence (SEQ ID NO:)		
14	VH1A	GGTFSSYALS (366)	GIIPFGCTANYAQRFG (368)	WSDQSYHYWHPYFDV (370)	VL1	SGSSSNIGSNYVS (371)	LMIYDNNQRPS (373)	QSWDLPEY (59)	10 +/- 5	14 +/- 3
17	VH5	GYSFTSYWIG (367)	IIYPGDSSTRYSPSPFG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QSYDPSHS K (61)	13 +/- 3	11 +/- 3
54	VH5	GYSFTSYWIG (367)	IIYPGDSSTRYSPSPFG (369)	YGFEXDILLEFN (34)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QSYDISGYP (77)	9 +/- 1	7
17-1	VH5	GYSFTSYWIG (367)	IIYPGDSSTRYSPSPFG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QAFDVAPNG K (376)	0.8	1.6
17-2	VH5	GYSFTSYWIG (367)	IIYPGDSSTRYSPSPFG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QAFVWPNV E (377)	1.3	1.1
17-3	VH5	GYSFTSYWIG (367)	IIYPGDSSTRYSPSPFG (369)	LTNYFDSIYYDH (18)	VL2	TGTSSDVGGYNYVS (363)	LMIYDVSNRPS (374)	QSFTVSPGA D (378)	1.9	3
54-1	VH5	GYSFTSYWIG (367)	IIYPGDSSTRYSPSPFG (369)	YGFEXDILLEFN (34)	VL2	TGTSSDLGGYNYVS (372)	LMIYAGNNRPS (375)	QAYDSSGYP (379)	2	3

- [155] The improvement gained by these different one-step maturation strategies was up to a factor of 16.3 with regard to affinity and 10 with regard to functional activity in the protease assay.

EXAMPLE 21

Conversion of anti-TIMP-1 Fab fragments into human IgG₁ molecules for use in the rat model of chronic carbon tetrachloride-induced liver fibrosis

- [156] Anti-TIMP-1 Fab fragments were converted into human IgG₁ molecules to create antibody molecules with prolonged *in vivo* half-lives for the use in the rat model of chronic carbon tetrachloride-induced liver fibrosis. This was done by cloning the heavy and light chain variable regions of the Fab into two separate vectors for mammalian IgG₁ expression (Krebs *et al.*, 2001)
- [157] Anti-rat TIMP-1 clone MS-BW-14 was chosen for the first *in vivo* study, and IgG₁ protein was produced by transient expression. Anti-human TIMP-1 clone MS-BW-3 was selected as a negative control IgG₁ and was also produced by transient expression. Purified IgG₁ proteins MS-BW-14 and MS-BW-3 were subjected to quality control in BIAcore™ and rat TIMP-1/rat MMP-13 assays. Bivalent affinity for rat TIMP-1 measured in BIAcore™ (chip density 500 RU, fitting model for bivalent analyte) is 0.2 nM for MS-BW-14, compared to 13 nM for the corresponding monovalent Fab fragment. This increase in affinity for the IgG₁ is due to the avidity effects caused by binding of bivalent IgG₁ to immobilized rat TIMP-1 protein on the BIAcore™ chip. As expected, the negative control IgG₁ MS-BW-3 showed no binding to rat TIMP-1 but bound to human TIMP-1 with a bivalent affinity of approximately 0.4 nM.
- [158] FIG. 12 shows the activity of MS-BW-14 Fab and IgG₁ and MS-BW-3 IgG₁ in a rat TIMP-1/rat MMP-13 assay. The IC₅₀ of MS-BW-14 Fab and IgG₁ are nearly identical. The avidity effect seen in BIAcore™ does not occur in this assay because, in contrast to

the BIAcore™ experiment, this assay is based on a monovalent interaction in solution between TIMP-1 and the IgG₁. As expected, MS-BW-3 has no effect on rat TIMP-1 binding to rat MMP-13 and thus is a suitable negative control for a rat *in vivo* study.

- [159] Affinity matured clone MS-BW-17-1 was then converted from a monovalent Fab fragment to a bivalent IgG₁. Protein was produced by stable transfection. Purified protein was subjected to quality control in BIAcore™ and rat TIMP-1/rat MMP-13 assays (FIG. 13). In BIAcore™ an increased bivalent affinity (avidity) of 0.04 nM for IgG₁ compared to 0.8 nM for monovalent Fab fragment was seen, whereas the activity in the rat TIMP-1/rat MMP-13 assay was comparable for IgG₁ and Fab as expected.

EXAMPLE 22

Cross-reactivity of anti-rat TIMP-1 IgG₁ MS-BW-17-1 with mouse TIMP-1

- [160] Species cross-reactivity of MS-BW-17-1 IgG₁ and Fab with mouse TIMP-1 was determined by BIAcore™ to investigate the feasibility of alternative *in vivo* models that use mice instead of rats. Although MS-BW-17-1 clearly bound to mouse TIMP-1 immobilized to the chip surface, the affinity of both Fab (180 nM) and IgG₁ (9 nM) was 225-fold weaker than the affinity to rat TIMP-1. As the interaction between mouse TIMP-1 and BW-17-1 IgG₁ in serum is most likely monovalent, the affinity of BW-17-1 Fab probably reflects the “real” affinity of this interaction. Therefore, the Fab affinity value should be considered when calculating the feasibility of using BW-17-1 IgG₁ in a mouse *in vivo* study.

EXAMPLE 23

Effect of Timp-1 antibody on the development of bleomycin-induced pulmonary fibrosis

- [161] The following example demonstrates the ability of a human anti-rat Timp-1 antibody (BW17.1) to prevent fibrotic collagen deposition in a bleomycin-induced rat lung fibrosis model.
- [162] Male Lewis rats (6 weeks of age) received a single intratracheal challenge with bleomycin (0.3 mg/rat, in saline) or vehicle (saline) on day 0. Fourteen days later, animals were euthanized, the lung excised, fixed, and processed for evaluation of lung fibrosis. Lung tissue sections were cut, and quantitative assessment by image analysis of lung collagen in lung tissue sections stained with Mason Trichrome stain performed.
- [163] Antibody administration: A 20 mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered subcutaneously on day -1. Subsequently, a 10mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered s.c. on days 2, 5, 8, and 11. The following five groups of animals were studied: Saline i.t. challenge + antibody vehicle (PBS); Saline i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + antibody vehicle (PBS); Bleomycin i.t. challenge + control antibody.
- [164] FIG. 14 shows the effect of the inhibitory effect of TIMP-1 antibody on bleomycin-induced lung fibrotic collagen.

EXAMPLE 24

Effect of BW-14 anti-TIMP-1 antibody in a rat model with CCl₄-induced liver fibrosis

- [165] Carbon tetrachloride (CCl₄) was used to induce liver fibrosis as described in Example 9. A single intravenous dose of 3 mg/kg BW-14 or control antibody BW-3, respectively,

was administered on day 19. At this time, total liver collagen (hydroxyproline determined according to Prockop and Udenfried) is already significantly increased by CCl₄, and fibrotic collagen rapidly accumulates during the following weeks. The rats were sacrificed on day 28. The treatment groups were: no CCl₄ + control antibody BW 3 (n=10 rats), CCl₄ + control antibody BW 3 (n=20 rats), and CCl₄ + BW 14 (n=20 rats).

- [166] The effect of control vs. TIMP-1 antibody as reflected in morphometric measurements of fibrous collagen (Sirius Red stained area as percentage of the total field) is shown in FIG. 15. Comparison of both control antibody treated groups shows that CCl₄ caused an approximately three-fold increase in collagen area. BW-14 antibody treatment reduced the pathological collagen increment by 26%. The lower fibrous collagen value of the CCl₄ + BW-14 group compared to the CCl₄ + BW-3 group was statistically significant (p< 0.05, Kolmogorow-Smirnow test).

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CLAIMS

1. A purified preparation of a human antibody, wherein the antibody:
binds to a tissue inhibitor of metalloprotease-1 (TIMP-1); and
neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.
2. The preparation of claim 1 wherein the MMP is human MMP-1.
3. The preparation of claim 2 wherein the MMP is rat MMP-13.
4. The preparation of claim 1 wherein the TIMP-1 is a human TIMP-1.
5. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.2 nM to about 0.5 nM, about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM.
6. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 M, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.
7. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC_{50} selected from the group consisting of about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM, and about 4 nM to about 11 nM.

8. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC_{50} selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.

9. The preparation of claim 4 wherein the K_d for binding to human TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the human TIMP-1 are approximately equal.

10. The preparation of claim 1 wherein the TIMP-1 is a rat TIMP-1.

11. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM.

12. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.

13. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC_{50} selected from the group consisting of about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3

nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM.

14. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC_{50} selected from the group consisting of about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.

15. The preparation of claim 10 wherein the K_d for binding to rat TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the rat TIMP-1 are approximately equal.

16. A purified preparation of a human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.

17. A purified preparation of a human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.

18. A purified preparation of a human antibody which comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10

and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

19. A purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID

NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

20. The purified preparation of claim 19 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.

21. The purified preparation of claim 19 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

22. A purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101,

SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NO:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

23. A pharmaceutical composition comprising:

a human antibody which (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1; and

a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23 wherein the MMP is human MMP-1.

25. The pharmaceutical composition of claim 23 wherein the MMP is rat MMP-13.

26. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a human TIMP-1.

27. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a rat TIMP-1.
28. The pharmaceutical composition of claim 23 wherein a K_d for binding to the TIMP-1 and an IC_{50} for neutralizing the MMP-1-inhibiting activity of the TIMP-1 are approximately equal.
29. A purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
30. The purified polynucleotide of claim 31 wherein the VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
31. A purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
32. The purified polynucleotide of claim 31 wherein the VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.
33. The purified polynucleotide of claim 31 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
34. The purified polynucleotide of claim 33 wherein the heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

35. The purified polynucleotide of claim 33 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

36. The purified polynucleotide of claim 35 wherein the light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.

37. An expression vector comprising the polynucleotide of claim 29.

38. An expression vector comprising the polynucleotide of claim 30.

39. An expression vector comprising the polynucleotide of claim 31.

40. An expression vector comprising the polynucleotide of claim 32.

41. An expression vector comprising the polynucleotide of claim 33.

42. An expression vector comprising the polynucleotide of claim 34.

43. An expression vector comprising the polynucleotide of claim 35.

44. An expression vector comprising the polynucleotide of claim 36.

45. A host cell comprising the expression vector of claim 37.

46. A host cell comprising the expression vector of claim 38.

47. A host cell comprising the expression vector of claim 39.

48. A host cell comprising the expression vector of claim 40.

49. A host cell comprising the expression vector of claim 41.

50. A host cell comprising the expression vector of claim 42.

51. A host cell comprising the expression vector of claim 43.

52. A host cell comprising the expression vector of claim 44.

53. A method of making a human antibody, comprising the steps of:
- culturing the host cell of claim 45 under conditions whereby the antibody is expressed; and
- purifying the human antibody from the host cell culture.
54. The method of claim 55 wherein the expression vector comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOS:183-357.
55. A method of decreasing an MMP-inhibiting activity of a TIMP-1, comprising the step of:
- contacting the TIMP-1 with a human antibody that binds to the TIMP-1, whereby the MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.
56. The method of claim 55 wherein the MMP is human MMP-1.
57. The method of claim 55 wherein the MMP is rat MMP-13.
58. The method of claim 55 wherein the TIMP-1 is a human TIMP-1.
59. The method of claim 55 wherein the TIMP-1 is a rat TIMP-1.
60. The method of claim 55 wherein the step of contacting is carried out in a cell-free system.
61. The method of claim 55 wherein the step of contacting is carried out in a cell culture system.
62. The method of claim 55 wherein the step of contacting is carried out *in vivo*.

63. The method of claim 55 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

64. A method of ameliorating symptoms of a disorder in which TIMP-1 is elevated, comprising the step of:

administering to a patient having the disorder an effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1, whereby symptoms of the disorder are ameliorated.

65. The method of claim 64 wherein the MMP is human MMP-1.

66. The method of claim 64 wherein the MMP is rat MMP-13.

67. The method of claim 64 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer.

68. The method of claim 64 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71,

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69. A method of detecting a TIMP-1 in a test preparation, comprising the steps of:
contacting the test preparation with a human antibody that specifically binds to the TIMP-1; and

assaying the test preparation for the presence of an antibody-TIMP-1 complex.

70. The method of claim 69 wherein the antibody comprises a detectable label.

71. The method of claim 69 wherein the antibody is bound to a solid support.

72. The method of claim 69 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID

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73. A method to aid in diagnosing a disorder in which a TIMP-1 level is elevated, comprising the steps of:

contacting a sample from a patient suspected of having the disorder with a human antibody that binds to TIMP-1; and

assaying for the presence of an antibody-TIMP-1 complex, whereby detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

74. The method of claim 73 wherein the antibody comprises a detectable label.

75. The method of claim 73 wherein the antibody is bound to a solid support.

76. The method of claim 73 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID

NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

77. The method of claim 73 wherein the sample is obtained from a tissue selected from the group consisting of colon, liver, heart, kidney, prostate, serum, and lung.

78. The method of claim 73 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome,

lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis.

Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

VL

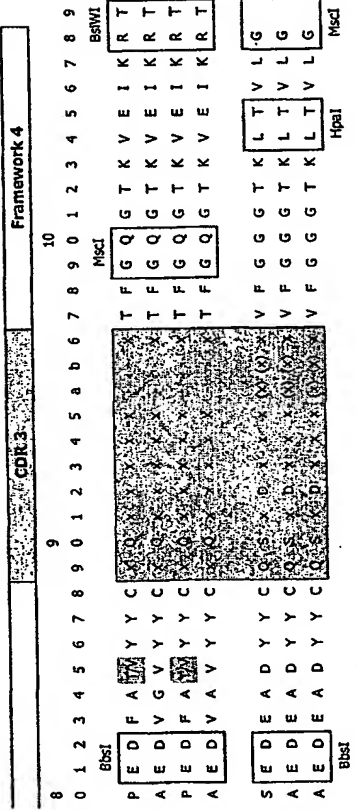
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Position		1																												2																												3																											
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		EcoRV																												PstI																																																							
VLk1		D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A	S	Q	S	L	F	H	S	N	G	X	A	Y	L	D																																													
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VL1		D	I	V	L	T	Q	P	P	-	S	V	S	G	A	P	G	Q	R	V	T	I	S	C	S	G	S	S	N	I	G	S	N	I	V	S																																																	
VL2		D	I	A	L	T	Q	P	A	-	S	V	S	G	S	P	G	Q	S	I	T	I	S	C	T	G	T	S	T	S	D	G	B	D	N	V	S																																																
VL3		D	I	E	L	T	Q	P	P	-	S	V	S	V	A	P	G	Q	T	A	R	I	S	C	S	G	D	A	I	G	D	T	N	K	V	A	S																																																
		EcoRV																												BspI																												SseAI																											

VH		Framework 1																		CDR1									
Position		1																		2									
		1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 a b 2 3 4 5 6 7 8																											
		MseI																		BspEI									
VH1A	Q V Q L	V Q S G A E V K K P G S S V K V S C K A	S S G T T S S V Y A S W V R																										
VH1B	Q V Q L	V Q S G A E V K K P G A S V K V S C K A	S S C L T T S S V Y M H W V R																										
VH2	Q V Q L	K E S G P A L V K P T Q T L T L T C T F S C P L S T S G V G S W I R																											
VH3	Q V Q L	V E S G G L V Q P G S L R L S C A S G H P S S L S G V A S W V R																											
VH4	Q V Q L	Q E S G P L V K P S E T L S L T C T V S C G T T S S V Y A S W V R																											
VH5	Q V Q L	V Q S G A E V K K P G E S L K I S C K G S G T T S S V Y A S W V R																											
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Fig. 1

[illegible][illegible]

Fig. 1, cont.



Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

VL

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1												2											
Position												3											
EcoRV												BstXI											
VL1	GAT	ATC	CAG	ATG	ACC	CAG	ACC	CGG	TCT	AGC	CTG	AGC	GCG	AGC	GTC	GAT	CGT	GTG	ACC	ATT	ACC	AGC	AGC
VL2	GAT	ATC	ATG	ATG	ACC	CAG	ACC	CGG	CTG	AGC	CTG	CCA	GTG	ACT	CCG	GCG	GAG	CGT	GCG	AGC	ATT	AGC	TGC
VL3	GAT	ATC	CTG	CTG	ACC	CAG	ACC	CGG	GCG	AGC	CTG	TCT	CCG	GCG	GAA	CGT	GCG	AGC	CGT	GCG	AGC	ATT	AGC
VL4	GAT	ATC	CTG	ATG	ACC	CAG	ACC	CGG	GAT	AGC	CTG	GCG	GTG	AGC	CTG	GCG	GAA	CGT	GCG	AGC	ATT	AGC	TGC
EcoRV												BstXI											
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VL2	GAT	ATC	GCA	CTG	ACC	CAG	ACC	CGG	CTT	TCA	GTG	AGC	GCG	TCA	CCA	GGT	CAG	AGC	ATT	AGC	ATT	AGC	TGC
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KpnI												KpnI											
KpnI												KpnI											

VH

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1												2											
Position												3											
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Fig. 2

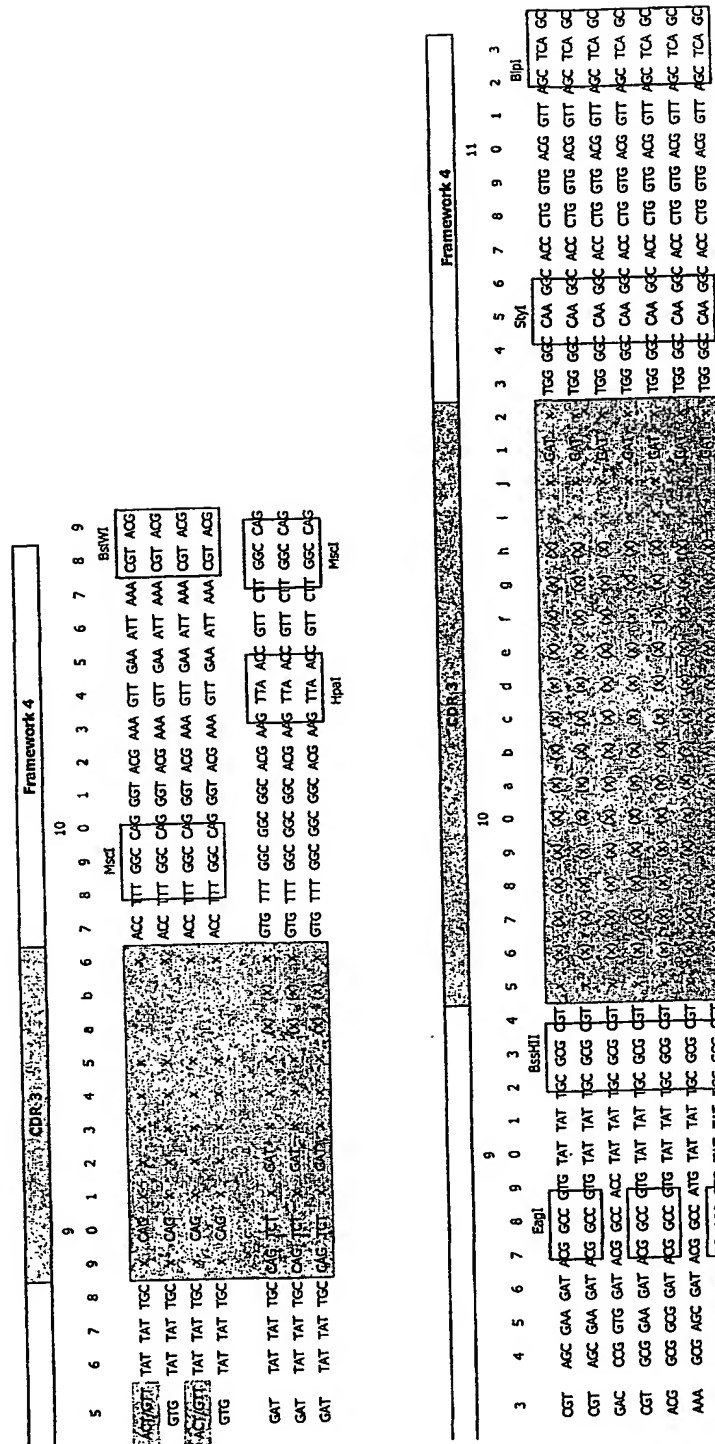


Fig. 2, cont.

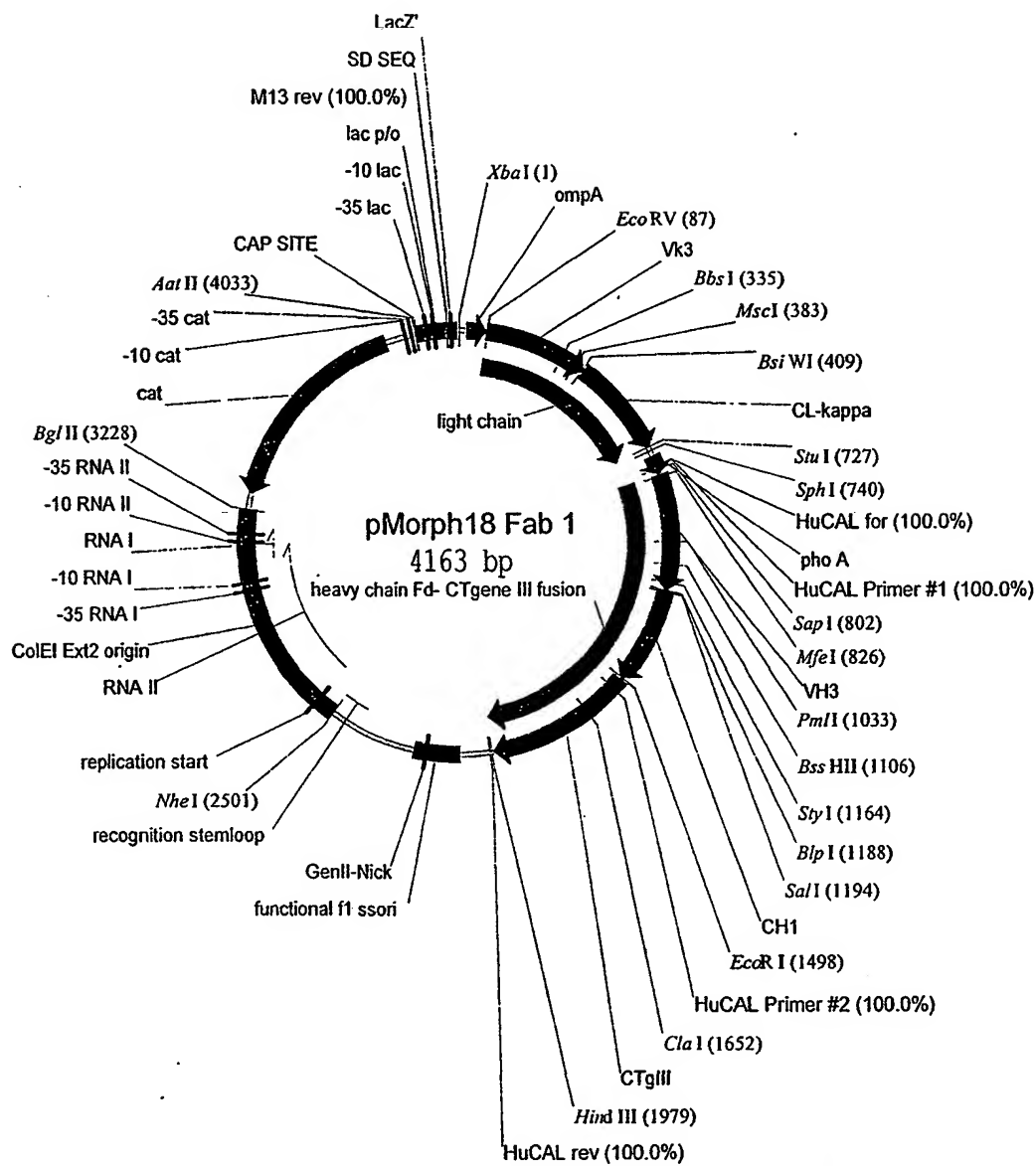


FIG. 3

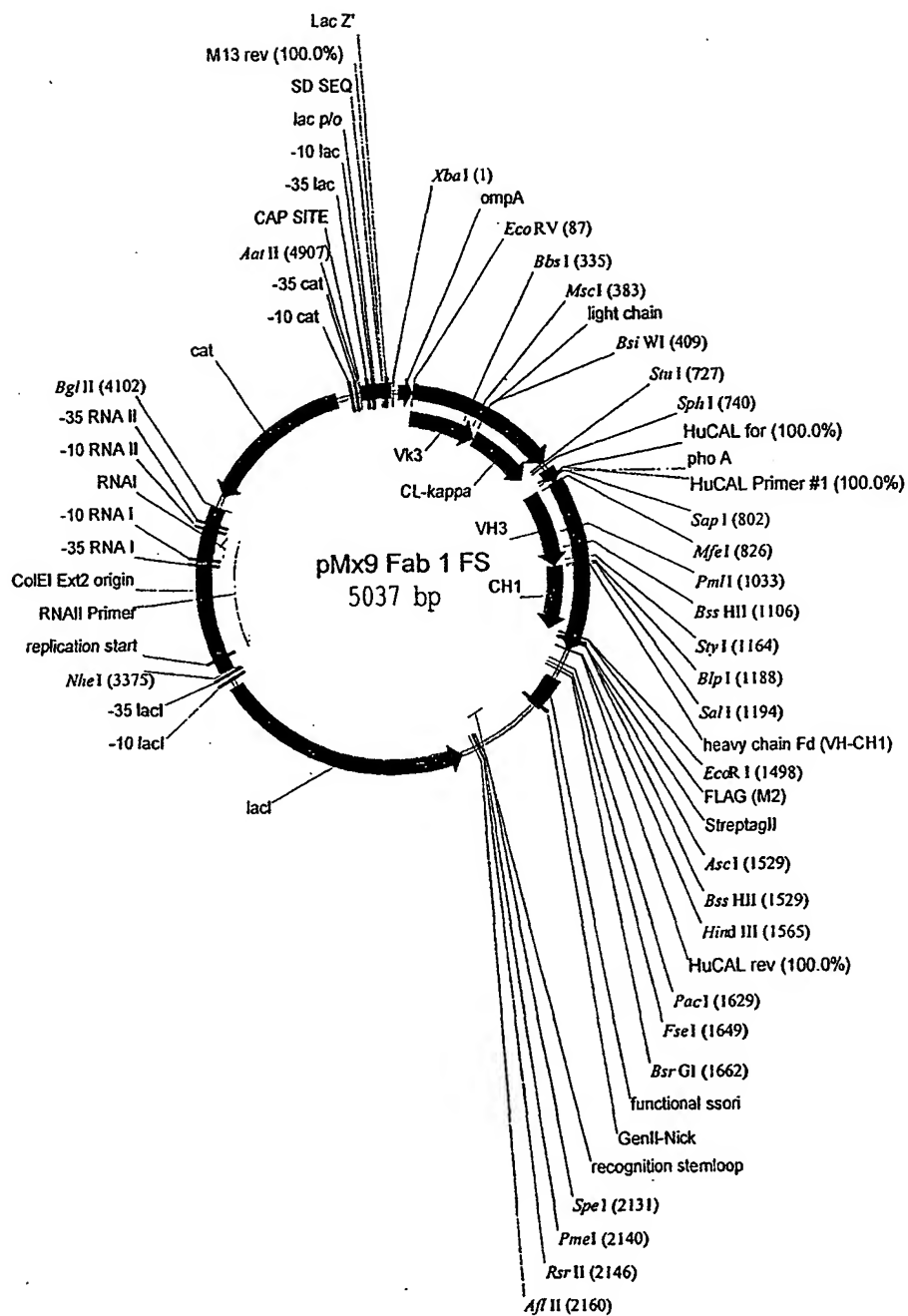


FIG. 4

FIG. 5

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      * * * ***** * * * . ***** * * *
      * * * ***** * * * . ***** * * *

TIMP1_human 135850     51 ALGDAADIRFVYTPAMFSVCGYFHRSHNRSEELIAGKLQDGLLHITCS 100
TIMP1_rat 1174697     51 AVGNATGFRFAYTPAMESLCGVVHKSONRSEELIAGRLRNGNLHITACS 100
      * * * . ** ***** * * * . ***** * * *
      * * * . ** ***** * * * . ***** * * *

TIMP1_human 135850    101 FVAPWNSLSLAQRGFTKTYTVGCEECTVFPCLSIPCKLQSGTHCLWTDQ 150
TIMP1_rat 1174697    101 FLVPWHNLSPAQQAFAVKTYSAGCGVCTVFPCSAIPCKLESDSSHCLWTDQ 150
      * * * . ** ***** * * * . ***** * * *
      * * * . ** ***** * * * . ***** * * *

TIMP1_human 135850    151 ILQSEKGFQSRHLACLPREPGLCTWQSLRSQIA 184
TIMP1_rat 1174697    151 ILNGSEKGYQSDHFACLPRNPDLCTWQYLGVSMTRSLPLAKAEA 194
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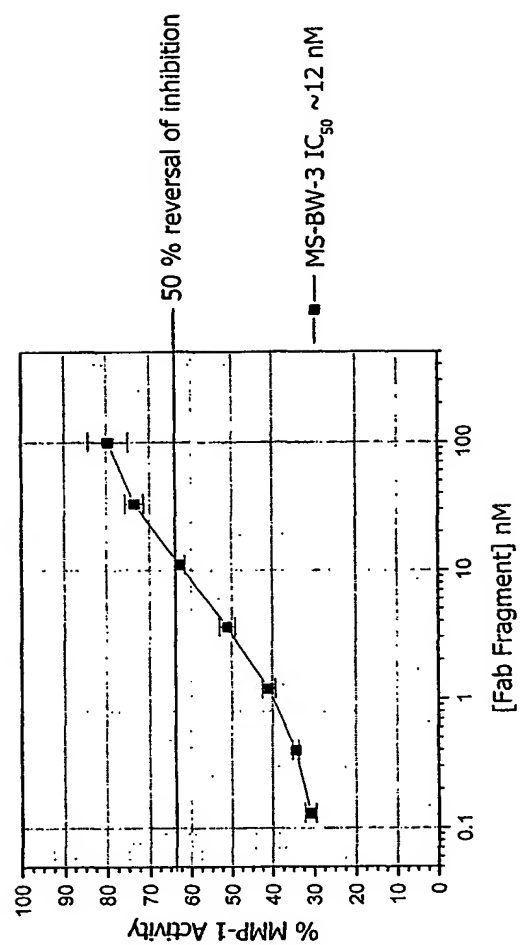


FIG. 6

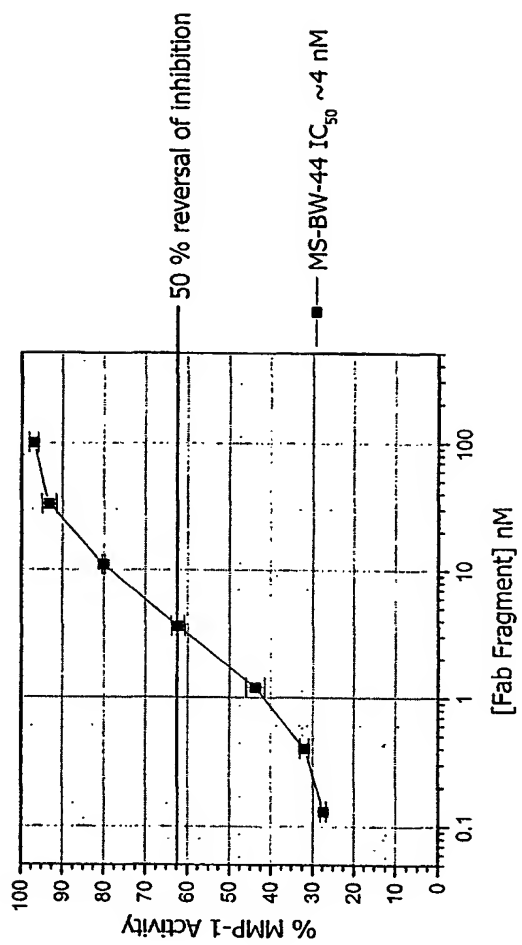


FIG. 7

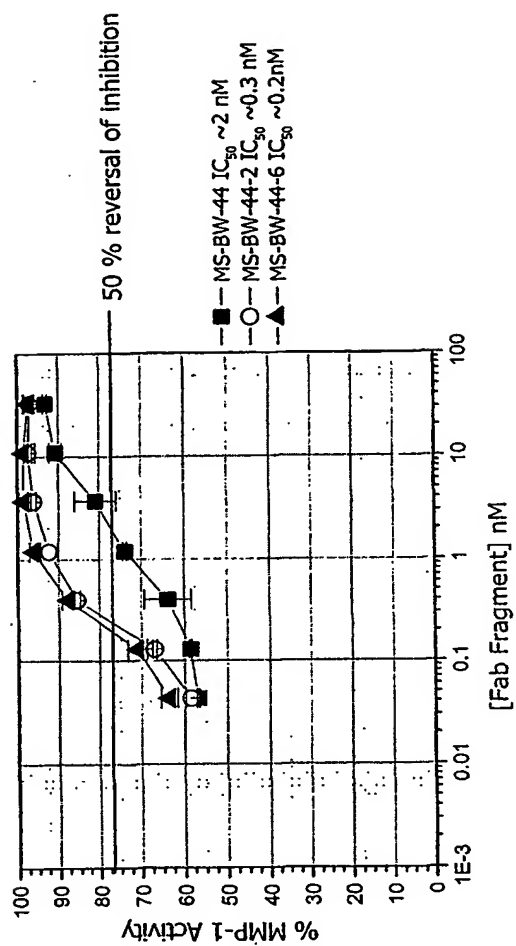


FIG. 8

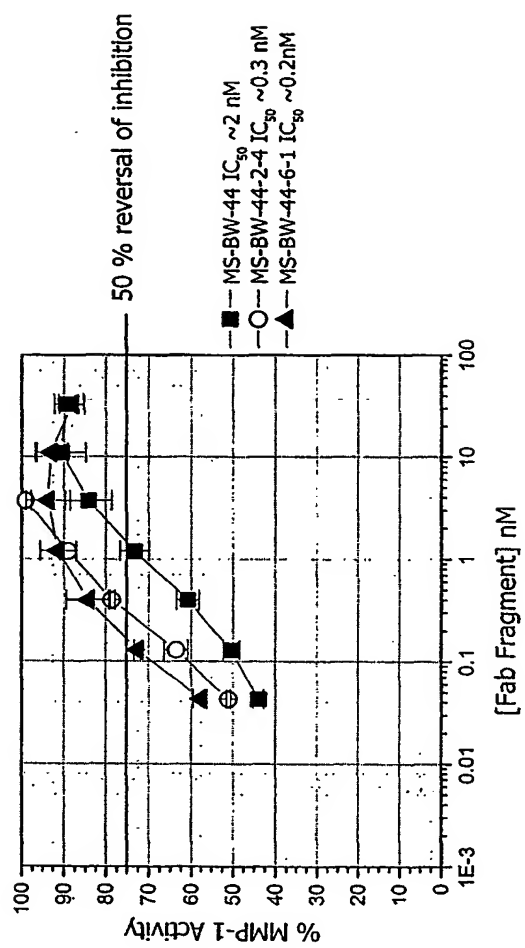


FIG. 9

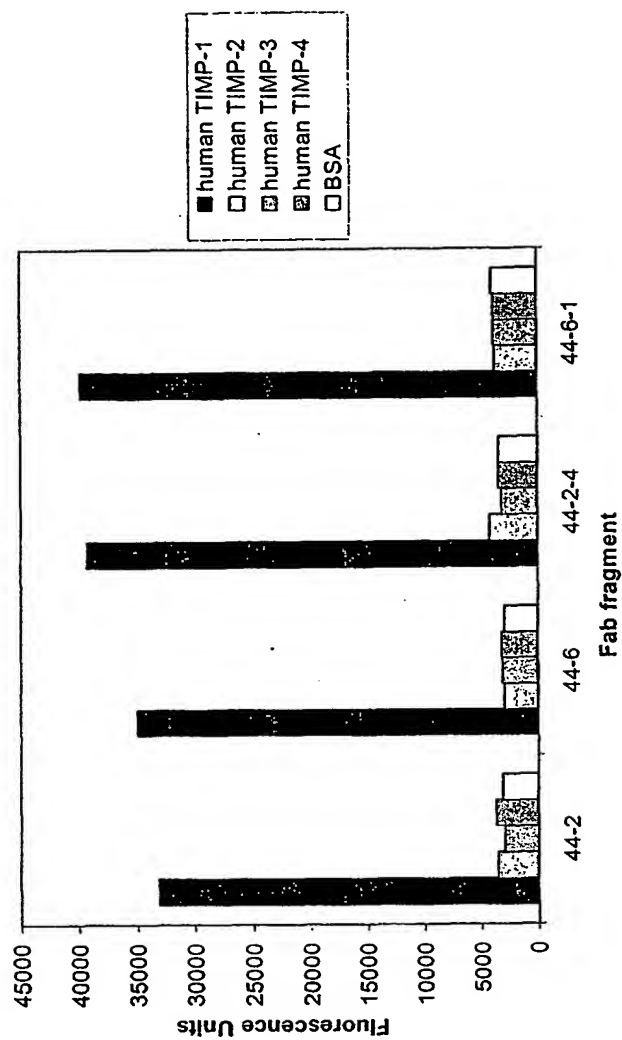


FIG. 10

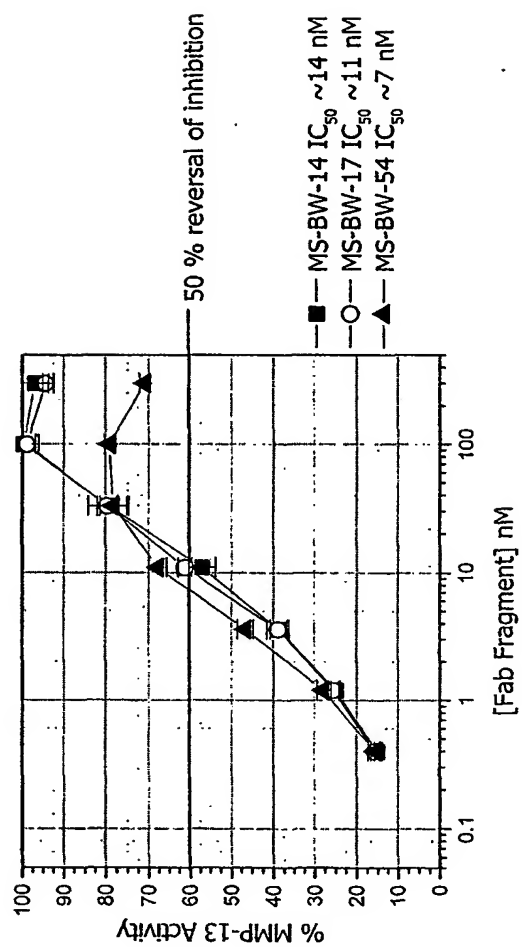


FIG. 11

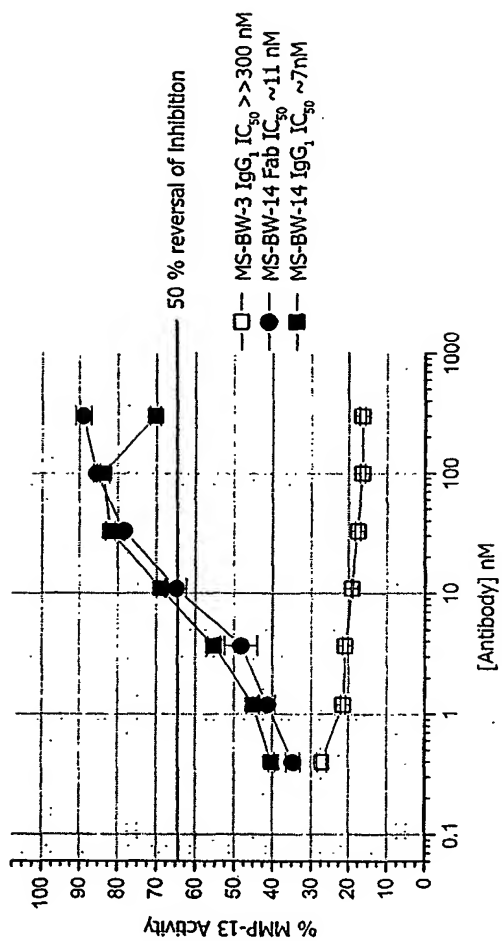


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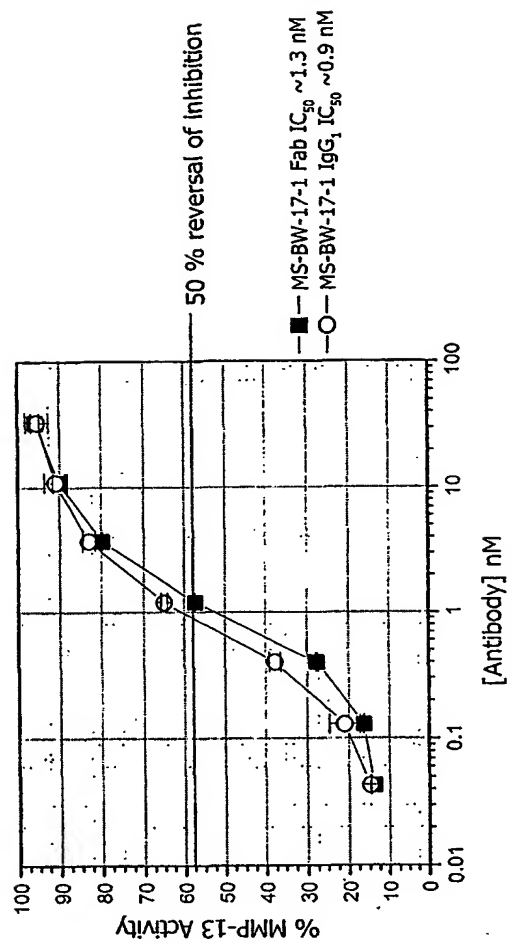


FIG. 13

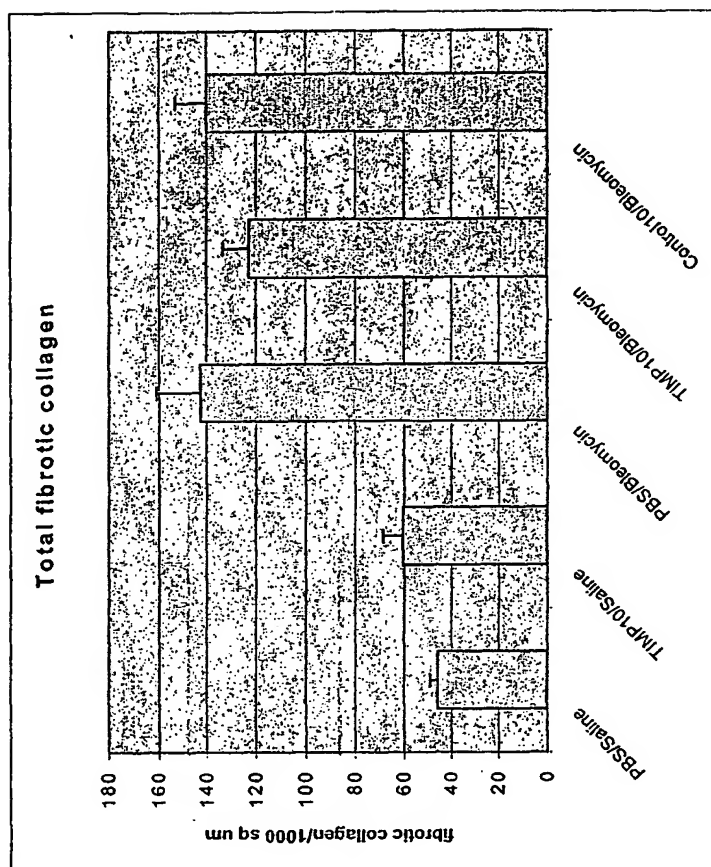
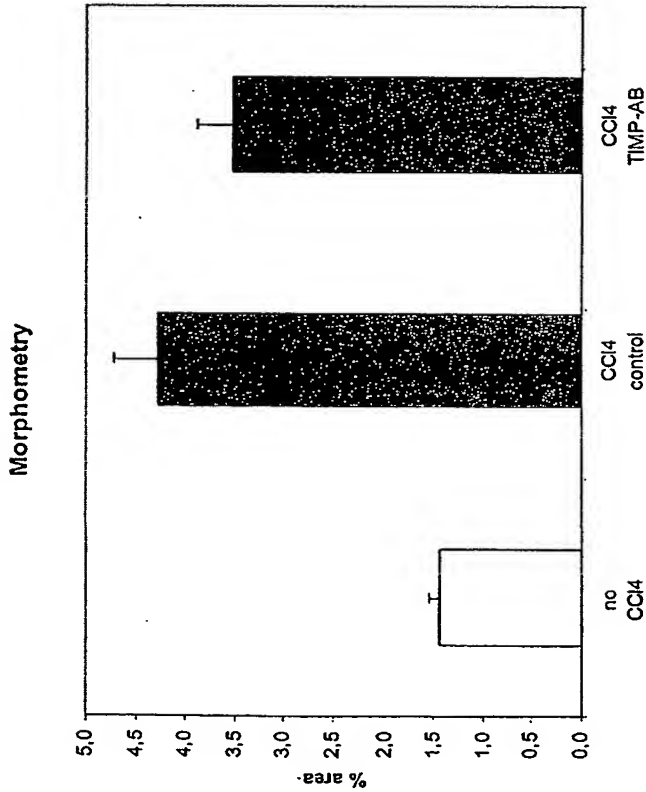


FIG. 14

FIG. 15



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<213> Homo sapiens

<400> 19

Leu Val Gly Gly Gly Tyr Asp Leu Met Phe Asp Ser
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<210> 20

<211> 13

<212> PRT

<213> Homo sapiens

<400> 20

Tyr Val Thr Tyr Gly Tyr Asp Asp Tyr His Phe Asp Tyr
1 5 10

<210> 21

<211> 6

<212> PRT

<213> Homo sapiens'

<400> 21

Ser Gly Tyr Leu Asp Tyr

1 5

<210> 22

<211> 18

<212> PRT

<213> Homo sapiens

<400> 22

Tyr Ile Gly Tyr Thr Asn Val Met Asp Ile Arg Pro Gly Tyr Phe Leu

1 5 10 15

Asp Tyr

<210> 23

<211> 12

<212> PRT

<213> Homo sapiens

<400> 23

Phe Arg Ala Tyr Gly Asp Asp Phe Tyr Phe Asp Val

1 5 10

<210> 24

<211> 15

<212> PRT

<213> Homo sapiens

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Xaa Met Trp Ser Asp Tyr Gly Gln Leu Val Lys Gly Gly Asp Ile

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<213> Homo sapiens

<400> 25

Tyr Tyr Val Thr Asp Thr Ala Tyr Phe Asp Tyr

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1                               5                               10
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<212> PRT
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His Asp Phe Asp Gly Ser Ile Phe Met Asp Phe
1                               5                               10

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<213> Homo sapiens

<400> 27
Tyr Ala Gly His Gln Tyr Glu Phe Phe Phe Asp Phe
1                               5                               10

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Leu Tyr Ala Asp Ala Asp Ile Tyr Phe Asp Tyr
1                               5                               10

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Thr Lys Tyr Val Gly Ser Glu Asp Val
1                               5

<210> 30
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Tyr Arg Tyr Pro His Met Phe Asp Phe
1                               5

<210> 31
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<213> Homo sapiens

<400> 31

Leu Phe Ala Gly Leu Glu Leu Tyr Phe Asp Tyr
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<211> 8

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<213> Homo sapiens

<400> 32

Gly Gly Phe Phe Asn Met Asp Tyr
1 5

<210> 33

<211> 10

<212> PRT

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<400> 33

Gly Tyr Ile Pro Tyr His Leu Phe Asp Tyr
1 5 10

<210> 34

<211> 12

<212> PRT

<213> Homo sapiens

<400> 34

Tyr Tyr Gly Phe Glu Tyr Asp Leu Leu Phe Asp Asn
1 5 10

<210> 35

<211> 8

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<213> Homo sapiens

<400> 35

Ile Thr Tyr Ile Gly Tyr Asp Phe
1 5

<210> 36

<211> 7

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<213> Homo sapiens

<400> 36

Gln Glu Trp Tyr Met Asp Tyr
1 5

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Leu Tyr Pro Glu Asp Leu Ile Tyr Phe Asp Tyr
1 5 10

<210> 38
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<212> PRT
<213> Homo sapiens

<400> 38
Trp Met Thr Pro Pro Gly His Tyr Tyr Gly Tyr Thr Phe Asp Val
1 5 10 15

<210> 39
<211> 12
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<213> Homo sapiens

<400> 39
Leu Arg Val His Asp Tyr Ala Met Tyr Phe Asp Leu
1 5 10

<210> 40
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<212> PRT
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<400> 40
Phe Val Ser Tyr Asn Gly Ser Val Pro Tyr Phe Asp Tyr
1 5 10

<210> 41
<211> 11
<212> PRT
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<400> 41
Ile Ile Gly Asp Tyr Val Ile Phe Phe Asp Val
1 5 10

<210> 42
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<400> 42
Leu Phe Thr Tyr Pro Phe Leu Tyr Phe Asp Val
1 5 10

<210> 43
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<400> 43
Ile Leu Thr Gly His Val Leu Leu Phe Asp Tyr
1 5 10

<210> 44
<211> 9
<212> PRT
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<400> 44
Gln Ser Tyr Asp Tyr Gln Gln Phe Thr
1 5

<210> 45
<211> 9
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<213> Homo sapiens

<400> 45
Gln Ser Tyr Asp Phe Lys Thr Tyr Leu
1 5

<210> 46
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<400> 46
Gln Ser Tyr Asp Phe Leu Arg Phe Ser
1 5

<210> 47
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<400> 47
Gln Ser Tyr Asp Phe Ile Asn Val Ile
1 5

<210> 48

<211> 9

<212> PRT

<213> Homo sapiens

<400> 48

Gln Ser Tyr Asp Phe Val Arg Phe Met

1

5

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<211> 9

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<213> Homo sapiens

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Gln Ser Tyr Asp Phe Tyr Lys Phe Asn

1

5

<210> 50

<211> 9

<212> PRT

<213> Homo sapiens

<400> 50

Gln Ser Tyr Asp Phe Arg Arg Phe Ser

1

5

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<211> 9

<212> PRT

<213> Homo sapiens

<400> 51

Gln Ser Arg Asp Phe Asn Arg Gly Pro

1

5

<210> 52

<211> 8

<212> PRT

<213> Homo sapiens

<400> 52

Gln Ser Tyr Asp Gln Arg Lys Trp

1

5

<210> 53

<211> 8

<212> PRT

<213> Homo sapiens

<400> 53

Gln Gln Leu Tyr Gly Thr Val Ser
1 5

<210> 54

<211> 9

<212> PRT

<213> Homo sapiens

<400> 54

Gln Ser Tyr Asp Gly Phe Lys Thr His
1 5

<210> 55

<211> 8

<212> PRT

<213> Homo sapiens

<400> 55

Gln Ser Tyr Asp Tyr Ser Leu Leu
1 5

<210> 56

<211> 8

<212> PRT

<213> Homo sapiens

<400> 56

Gln Ser Tyr Asp Phe Asn Phe His
1 5

<210> 57

<211> 10

<212> PRT

<213> Homo sapiens

<400> 57

Gln Ser Tyr Asp Met Ile Ala Arg Tyr Pro
1 5 10

<210> 58

<211> 10

<212> PRT

<213> Homo sapiens

<400> 58

Gln Ser Trp Asp Ile His Pro Phe Asp Val
1 5 10

<210> 59

<211> 8
<212> PRT
<213> Homo sapiens

<400> 59
Gln Ser Trp Asp Leu Glu Pro Tyr
1 5

<210> 60
<211> 9
<212> PRT
<213> Homo sapiens

<400> 60
Gln Ser Tyr Asp Val Leu Asp Ser Glu
1 5

<210> 61
<211> 10
<212> PRT
<213> Homo sapiens

<400> 61
Gln Ser Tyr Asp Pro Ser His Pro Ser Lys
1 5 10

<210> 62
<211> 8
<212> PRT
<213> Homo sapiens

<400> 62
Gln Ser Tyr Asp Asp Met Gln Phe
1 5

<210> 63
<211> 9
<212> PRT
<213> Homo sapiens

<400> 63
Gln Ser Trp Asp Ile Asn His Ala Ile
1 5

<210> 64
<211> 9
<212> PRT
<213> Homo sapiens

<400> 64

Gln Ser Tyr Asp Tyr Tyr Asp Tyr Gly
1 5

<210> 65
<211> 8
<212> PRT
<213> Homo sapiens

<400> 65
Gln Gln Ala Asn Asp Phe Pro Ile
1 5

<210> 66
<211> 10
<212> PRT
<213> Homo sapiens

<400> 66
Gln Ser Trp Asp Asn Leu Lys Met Pro Val
1 5 10

<210> 67
<211> 10
<212> PRT
<213> Homo sapiens

<400> 67
Gln Ser Tyr Asp Val Phe Pro Ile Asn Arg
1 5 10

<210> 68
<211> 7
<212> PRT
<213> Homo sapiens

<400> 68
Gln Ser Asp Leu Tyr Phe Pro
1 5

<210> 69
<211> 8
<212> PRT
<213> Homo sapiens

<400> 69
Gln Ser Tyr Asp Val Thr Pro Arg
1 5

<210> 70
<211> 9

<212> PRT

<213> Homo sapiens

<400> 70

Gln Ser Tyr Asp Pro Val Gly Phe Pro
1 5

<210> 71

<211> 8

<212> PRT

<213> Homo sapiens

<400> 71

Gln Ser Tyr Asp Leu Ser Pro Arg
1 5

<210> 72

<211> 10

<212> PRT

<213> Homo sapiens

<400> 72

Gln Ser Tyr Asp Phe Ser His Tyr Phe Phe
1 5 10

<210> 73

<211> 9

<212> PRT

<213> Homo sapiens

<400> 73

Gln Ser Tyr Asp Leu Arg Tyr Ser His
1 5

<210> 74

<211> 8

<212> PRT

<213> Homo sapiens

<400> 74

Gln Ser Tyr Asp Leu Arg Asn Arg
1 5

<210> 75

<211> 9

<212> PRT

<213> Homo sapiens

<400> 75

Gln Ser Tyr Asp Phe Thr Tyr Gly Ser

1 5

<210> 76
<211> 8
<212> PRT
<213> Homo sapiens

<400> 76
Gln Gln Phe Asn Asp Ser Pro Tyr
1 5

<210> 77
<211> 9
<212> PRT
<213> Homo sapiens

<400> 77
Gln Ser Tyr Asp Ile Ser Gly Tyr Pro
1 5

<210> 78
<211> 10
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<400> 78
Gln Ser Arg Asp Leu Tyr Tyr Val Tyr Tyr
1 5 10

<210> 79
<211> 8
<212> PRT
<213> Homo sapiens

<400> 79
Gln Ser Tyr Asp Arg Ser Met Trp
1 5

<210> 80
<211> 9
<212> PRT
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<400> 80
Gln Ser Trp Asp Val Gln Thr Asp Lys
1 5

<210> 81
<211> 9
<212> PRT

<213> Homo sapiens

<400> 81

Gln Ser Trp Asp Pro Ser His Tyr Tyr
1 5

<210> 82

<211> 9

<212> PRT

<213> Homo sapiens

<400> 82

Gln Ser Tyr Asp Ile Met Pro Glu Arg
1 5

<210> 83

<211> 9

<212> PRT

<213> Homo sapiens

<400> 83

Gln Ser Met Asp Phe Arg Leu Met His
1 5

<210> 84

<211> 9

<212> PRT

<213> Homo sapiens

<400> 84

Gln Ser Phe Asp Met Ile His Pro Tyr
1 5

<210> 85

<211> 7

<212> PRT

<213> Homo sapiens

<400> 85

Gln Ser Asp Phe Pro Val Met
1 5

<210> 86

<211> 7

<212> PRT

<213> Homo sapiens

<400> 86

Gln Ser Asp Asn Pro Tyr Leu
1 5

<210> 87
<211> 11
<212> PRT
<213> Homo sapiens

<400> 87
Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 88
<211> 12
<212> PRT
<213> Homo sapiens

<400> 88
Cys Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 89
<211> 12
<212> PRT
<213> Homo sapiens

<400> 89
Ser Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
1 5 10

<210> 90
<211> 13
<212> PRT
<213> Homo sapiens

<400> 90
Ser Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe Cys
1 5 10

<210> 91
<211> 10
<212> PRT
<213> Homo sapiens

<400> 91
Cys Glu Val Asn Gln Thr Thr Leu Tyr Gln
1 5 10

<210> 92
<211> 12
<212> PRT
<213> Homo sapiens

<400> 92

Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg
1 5 10

<210> 93

<211> 16

<212> PRT

<213> Homo sapiens

<400> 93

Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg Ser His Asn Arg
1 5 10 15

<210> 94

<211> 17

<212> PRT

<213> Homo sapiens

<400> 94

Cys Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn
1 5 10 15
Arg

<210> 95

<211> 17

<212> PRT

<213> Homo sapiens

<400> 95

Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn Arg
1 5 10 15
Cys

<210> 96

<211> 12

<212> PRT

<213> Homo sapiens

<400> 96

Cys Leu Trp Thr Asp Gln Leu Leu Gln Gly Ser Glu
1 5 10

<210> 97

<211> 215

<212> PRT

<213> Homo sapiens

<400> 97

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Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20           25           30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
      50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
      65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Gln
      85           90           95
Gln Phe Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100          105          110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
      115          120          125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
      130          135          140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
      145          150          155          160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
      165          170          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180          185          190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
      195          200          205
Thr Val Ala Pro Thr Glu Ala
      210          215

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<210> 98

<211> 215

<212> PRT

<213> Homo sapiens

<400> 98

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Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20           25           30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
      50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
      65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Lys
      85           90           95
Thr Tyr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100          105          110

```

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 99

<211> 211

<212> PRT

<213> Homo sapiens

<400> 99

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Leu
 85 90 95
 Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala
 210

<210> 100
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 100
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ile
 85 90 95
 Asn Val Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 101
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 101
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```

65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Val
      85          90          95
Arg Phe Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100          105          110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
      115          120          125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
      130          135          140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145          150          155          160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
      165          170          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180          185          190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
      195          200          205
Thr Val Ala Pro Thr Glu Ala
      210          215

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<210> 102

<211> 215

<212> PRT

<213> Homo sapiens

<400> 102

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Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1      5      10      15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20      25      30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35      40      45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
      50      55      60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65      70      75      80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Tyr
      85      90      95
Lys Phe Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100      105      110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
      115      120      125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
      130      135      140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145      150      155      160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
      165      170      175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180      185      190

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Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 103
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 103
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Arg
 85 90 95
 Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 104
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 104
 Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1 5 10 15
 Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
 20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
 65 70 75 80
 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Phe Asn Arg
 85 90 95
 Gly Pro Val Phe Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
 100 105 110
 Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
 115 120 125
 Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
 130 135 140
 Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Pro Val Lys Ala
 145 150 155 160
 Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
 165 170 175
 Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
 180 185 190
 Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
 195 200 205
 Val Ala Pro Thr Glu Ala
 210

<210> 105

<211> 213

<212> PRT

<213> Homo sapiens

<400> 105

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1 5 10 15
 Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
 20 25 30
 Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
 65 70 75 80
 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gln Arg Lys
 85 90 95
 Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
 100 105 110
 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
 115 120 125
 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
 130 135 140
 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly

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<210> 106
<211> 215
<212> PRT
<213> Homo sapiens
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<210> 107
<211> 214
<212> PRT
<213> Homo sapiens
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<400> 107

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Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1           5           10           15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
      20           25           30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
      35           40           45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50           55           60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
 65           70           75           80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gly Phe Lys
      85           90           95
Thr His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
      100          105          110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
      115          120          125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
      130          135          140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
      145          150          155          160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
      165          170          175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
      180          185          190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
      195          200          205
Val Ala Pro Thr Glu Ala
      210

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<210> 108

<211> 211

<212> PRT

<213> Homo sapiens

<400> 108

```

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1           5           10           15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
      20           25           30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
      35           40           45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50           55           60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65           70           75           80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Ser Leu Leu Val
      85           90           95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
      100          105          110

```

```

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
      115              120              125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
      130              135              140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145      150              155              160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
      165              170              175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
      180              185              190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
      195              200              205
Thr Glu Ala
      210

```

<210> 109
 <211> 211
 <212> PRT
 <213> Homo sapiens

```

<400> 109
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1      5              10              15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
      20              25              30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
      35              40              45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
      50              55              60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
      65              70              75              80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Asn Phe His Val
      85              90              95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
      100              105              110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
      115              120              125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
      130              135              140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145      150              155              160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
      165              170              175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
      180              185              190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
      195              200              205
Thr Glu Ala
      210

```

<210> 110
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 110
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Met Ile
 85 90 95
 Ala Arg Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110
 Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125
 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140
 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
 145 150 155 160
 Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175
 Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190
 His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200 205
 Lys Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 111
 <211> 213
 <212> PRT
 <213> Homo sapiens

<400> 111
 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
 20 25 30
 Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu


```

65          70          75          80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile His Pro Phe Asp
      85          90          95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
      100          105          110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
      115          120          125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
      130          135          140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145          150          155          160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
      165          170          175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
      180          185          190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
      195          200          205
Ala Pro Thr Glu Ala
      210

```

<210> 112
 <211> 213
 <212> PRT
 <213> Homo sapiens

```

<400> 112
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
 1          5          10          15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
      20          25          30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
      35          40          45
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
      50          55          60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65          70          75          80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Leu Glu Pro
      85          90          95
Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
      100          105          110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
      115          120          125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
      130          135          140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145          150          155          160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
      165          170          175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
      180          185          190

```

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195 200 205
 Ala Pro Thr Glu Ala
 210

<210> 113
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 113
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Leu
 85 90 95
 Asp Ser Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 114
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 114
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30

```

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
  35          40          45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
  50          55          60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
  65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Pro Ser
      85          90          95
His Pro Ser Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
      100          105          110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
      115          120          125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
  130          135          140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
  145          150          155          160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
      165          170          175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
      180          185          190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
  195          200          205
Lys Thr Val Ala Pro Thr Glu Ala
  210          215

```

<210> 115

<211> 214

<212> PRT

<213> Homo sapiens

<400> 115

```

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
  1          5          10          15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
  20          25          30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
  35          40          45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
  50          55          60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
  65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asp Met
      85          90          95
Gln Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
      100          105          110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
      115          120          125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
  130          135          140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala

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145          150          155          160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
          165          170          175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
          180          185          190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
          195          200          205
Val Ala Pro Thr Glu Ala
          210

```

```

<210> 116
<211> 215
<212> PRT
<213> Homo sapiens

```

```

<400> 116
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1          5          10          15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20          25          30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
          35          40          45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
          50          55          60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
          65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile Asn
          85          90          95
His Ala Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
          100          105          110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
          115          120          125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
          130          135          140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
          145          150          155          160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
          165          170          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
          180          185          190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
          195          200          205
Thr Val Ala Pro Thr Glu Ala
          210          215

```

```

<210> 117
<211> 215
<212> PRT
<213> Homo sapiens

```

<400> 117

```

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20           25           30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Tyr
      85           90           95
Asp Tyr Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100           105           110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
      115           120           125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
      130           135           140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145           150           155           160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
      165           170           175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180           185           190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
      195           200           205
Thr Val Ala Pro Thr Glu Ala
      210           215

```

<210> 118

<211> 215

<212> PRT

<213> Homo sapiens

<400> 118

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
      20           25           30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
      35           40           45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50           55           60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65           70           75           80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Asn Asp Phe Pro
      85           90           95
Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
      100           105           110

```

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 Ser Phe Asn Arg Gly Glu Ala
 210 215

<210> 119

<211> 216

<212> PRT

<213> Homo sapiens

<400> 119

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Asn Leu
 85 90 95
 Lys Met Pro Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110
 Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125
 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140
 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
 145 150 155 160
 Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175
 Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190
 His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200 205
 Lys Thr Val-Ala Pro Thr Glu Ala
 210 215

<210> 120
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 120
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Phe
 85 90 95
 Pro Ile Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110
 Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125
 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140
 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
 145 150 155 160
 Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175
 Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190
 His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200 205
 Lys Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 121
 <211> 213
 <212> PRT
 <213> Homo sapiens

<400> 121
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```

65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Leu Tyr Phe
85          90          95
Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100        105        110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115        120        125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130        135        140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145        150        155        160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165        170        175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180        185        190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195        200        205
Ala Pro Thr Glu Ala
210

```

<210> 122

<211> 214

<212> PRT

<213> Homo sapiens

<400> 122

```

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1          5          10          15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20        25        30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35        40        45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50        55        60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65        70        75        80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Thr
85        90        95
Pro Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100       105       110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115       120       125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130       135       140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145       150       155       160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165       170       175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180       185       190

```


Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
 195 200 205
 Val Ala Pro Thr Glu Ala
 210

<210> 123
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 123
 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
 20 25 30
 Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 Asp Glu Ala Asp Tyr Cys Gln Ser Arg Asp Pro Val Gly Phe Pro
 85 90 95
 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
 100 105 110
 Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
 115 120 125
 Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
 130 135 140
 Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
 145 150 155 160
 Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
 165 170 175
 Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
 180 185 190
 Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
 195 200 205
 Pro Thr Glu Ala
 210

<210> 124
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 124
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30

```

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
   35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
   50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
   65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Ser
           85           90           95
Pro Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
           100          105          110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
           115          120          125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
           130          135          140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
   145           150           155           160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
           165          170          175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
           180          185          190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
           195          200          205
Val Ala Pro Thr Glu Ala
           210

```

<210> 125
 <211> 216
 <212> PRT
 <213> Homo sapiens

```

<400> 125
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
   1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
           20           25           30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
           35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
           50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
           65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ser
           85           90           95
His Tyr Phe Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
           100          105          110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
           115          120          125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
           130          135          140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val

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145          150          155          160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
          165          170          175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
          180          185          190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
          195          200          205
Lys Thr Val Ala Pro Thr Glu Ala
          210          215

```

<210> 126
 <211> 212
 <212> PRT
 <213> Homo sapiens

```

<400> 126
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1          5          10          15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
          20          25          30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
          35          40          45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
          50          55          60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
          65          70          75          80
Asp Glu Ala Asp Tyr Cys Gln Ser Tyr Asp Leu Arg Tyr Ser His
          85          90          95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
          100          105          110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
          115          120          125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
          130          135          140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
          145          150          155          160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
          165          170          175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
          180          185          190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
          195          200          205
Pro Thr Glu Ala
          210

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<210> 127
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 127

```

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20           25           30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
      50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
      65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Arg
      85           90           95
Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
      100          105          110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
      115          120          125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
      130          135          140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
      145          150          155          160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
      165          170          175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
      180          185          190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
      195          200          205
Val Ala Pro Thr Glu Ala
      210

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<210> 128

<211> 215

<212> PRT

<213> Homo sapiens

<400> 128

```

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20           25           30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
      50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
      65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Thr
      85           90           95
Tyr Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100          105          110

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Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    115                120                125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                135                140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                150                155                160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
    165                170                175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
    180                185                190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
    195                200                205
Thr Val Ala Pro Thr Glu Ala
    210                215

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<210> 129
<211> 215
<212> PRT
<213> Homo sapiens

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<400> 129
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1                5                10                15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
    20                25                30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
    35                40                45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                55                60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
    65                70                75                80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Asn Asp Ser Pro
    85                90                95
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
    100                105                110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
    115                120                125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                135                140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                150                155                160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
    165                170                175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
    180                185                190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
    195                200                205
Ser Phe Asn Arg Gly Glu Ala
    210                215

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<210> 130
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 130
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Ser
 85 90 95
 Gly Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 131
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 131
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```

65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Leu Tyr
      85          90          95
Tyr Val Tyr Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
      100          105          110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
      115          120          125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
      130          135          140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
      145          150          155          160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
      165          170          175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
      180          185          190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
      195          200          205
Lys Thr Val Ala Pro Thr Glu Ala
      210          215

```

<210> 132
 <211> 211
 <212> PRT
 <213> Homo sapiens

```

<400> 132
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1          5          10          15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
      20          25          30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
      35          40          45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
      50          55          60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65          70          75          80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Ser Met Trp Val
      85          90          95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
      100          105          110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
      115          120          125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
      130          135          140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
      145          150          155          160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
      165          170          175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
      180          185          190

```

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
 195 200 205
 Thr Glu Ala
 210

<210> 133
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 133
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Val Gln
 85 90 95
 Thr Asp Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 Thr Val Ala Pro Thr Glu Ala
 210 215

<210> 134
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 134
 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
 20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 Asp Glu Ala Asp Tyr Cys Gln Ser Trp Asp Pro Ser His Tyr Tyr
 85 90 95
 Val Phe Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
 100 105 110
 Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
 115 120 125
 Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
 130 135 140
 Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
 145 150 155 160
 Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
 165 170 175
 Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
 180 185 190
 Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
 195 200 205
 Pro Thr Glu Ala
 210

<210> 135

<211> 215

<212> PRT

<213> Homo sapiens

<400> 135

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Met
 85 90 95
 Pro Glu Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys

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145          150          155          160
Ala Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
          165          170          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
          180          185          190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
          195          200          205
Thr Val Ala Pro Thr Glu Ala
          210          215

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<210> 136

<211> 215

<212> PRT

<213> Homo sapiens

<400> 136

```

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1          5          10          15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20          25          30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
          35          40          45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
          50          55          60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
          65          70          75          80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Met Asp Phe Arg
          85          90          95
Leu Met His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
          100          105          110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
          115          120          125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
          130          135          140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
          145          150          155          160
Ala Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
          165          170          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
          180          185          190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
          195          200          205
Thr Val Ala Pro Thr Glu Ala
          210          215

```

<210> 137

<211> 215

<212> PRT

<213> Homo sapiens

<400> 137

```

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20           25           30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Met Ile
      85           90           95
His Pro Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
      100          105          110
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
      115          120          125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
      130          135          140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145          150          155          160
Ala Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
      165          170          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180          185          190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
      195          200          205
Thr Val Ala Pro Thr Glu Ala
      210          215

```

<210> 138

<211> 213

<212> PRT

<213> Homo sapiens

<400> 138

```

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1           5           10           15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20           25           30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35           40           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50           55           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65           70           75           80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Phe Pro Val
      85           90           95
Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
      100          105          110

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Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
 115 120 125
 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
 130 135 140
 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
 145 150 155 160
 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
 165 170 175
 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
 180 185 190
 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195 200 205
 Ala Pro Thr Glu Ala
 210

<210> 139

<211> 213

<212> PRT

<213> Homo sapiens

<400> 139

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Asn Pro Tyr
 85 90 95
 Leu Val Phe Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
 100 105 110
 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
 115 120 125
 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
 130 135 140
 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
 145 150 155 160
 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
 165 170 175
 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
 180 185 190
 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195 200 205
 Ala Pro Thr Glu Ala
 210

<210> 140
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 140
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Phe Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 115 120 125
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 130 135 140
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 145 150 155 160
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 165 170 175
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 180 185 190
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215

<210> 141
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 141
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

```

65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85          90          95
Ala Arg Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100         105         110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115         120         125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130         135         140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145         150         155         160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165         170         175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180         185         190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195         200         205
Lys Lys Val Glu Pro Lys Ser Glu Phe
210         215

```

<210> 142

<211> 217

<212> PRT

<213> Homo sapiens

<400> 142

```

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1          5          10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20         25         30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35         40         45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50         55         60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65         70         75         80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85         90         95
Ala Arg Phe Leu Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100        105        110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115        120        125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130        135        140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145        150        155        160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165        170        175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180        185        190

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Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 195 200 205
 Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215

<210> 143
 <211> 221
 <212> PRT
 <213> Homo sapiens

<400> 143
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Phe Pro Ile Asp Ala Asp Ser Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 115 120 125
 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140
 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160
 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 165 170 175
 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190
 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205
 Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 144
 <211> 218
 <212> PRT
 <213> Homo sapiens

<400> 144
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Gly His Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
 100 105 110
 Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
 115 120 125
 Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
 130 135 140
 Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
 145 150 155 160
 Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
 165 170 175
 Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
 180 185 190
 Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
 195 200 205
 Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215

<210> 145

<211> 222

<212> PRT

<213> Homo sapiens

<400> 145

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Trp Arg Gly Leu Ser Phe Asp Ile Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 130 135 140
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn


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145          150          155          160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
          165          170          175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
          180          185          190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
          195          200          205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
          210          215          220

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<210> 146
 <211> 217
 <212> PRT
 <213> Homo sapiens

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<400> 146
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
  1          5          10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
          20          25          30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
          50          55          60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
          65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
          85          90          95
Ala Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
          100          105          110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
          115          120          125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
          130          135          140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
          145          150          155          160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
          165          170          175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
          180          185          190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
          195          200          205
Lys Lys Val Glu Pro Lys Ser Glu Phe
          210          215

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<210> 147
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 147

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Gly Leu Tyr Trp Ala Val Tyr Pro Tyr Phe Asp Phe Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 148

<211> 224

<212> PRT

<213> Homo sapiens

<400> 148

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Leu Asp Thr Tyr Tyr Pro Asp Leu Phe Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 149
 <211> 220
 <212> PRT
 <213> Homo sapiens

<400> 149
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Tyr Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125
 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190
 Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205
 Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe

210

215

220

<210> 150

<211> 224

<212> PRT

<213> Homo sapiens

<400> 150

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Met Ala Tyr Met Ala Glu Ala Ile Asp Val Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 151

<211> 230

<212> PRT

<213> Homo sapiens

<400> 151

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe

50		55		60	
Gln Gly Arg Val Thr	Met Thr Arg Asp Thr	Ser Ile Ser Thr	Ala Tyr		
65	70	75	80		
Met Glu Leu Ser Ser	Leu Arg Ser Glu Asp Thr	Ala Val Tyr Tyr	Cys		
	85	90	95		
Ala Arg Leu Val Gly	Ile Val Gly Tyr Lys Pro	Asp Glu Leu Leu	Tyr		
	100	105	110		
Phe Asp Val Trp Gly	Gln Gly Thr Leu Val Thr	Val Ser Ser Ala	Ser		
	115	120	125		
Thr Lys Gly Pro Ser	Val Phe Pro Leu Ala Pro	Ser Ser Lys Ser	Thr		
	130	135	140		
Ser Gly Gly Thr Ala	Ala Leu Gly Cys Leu Val	Lys Asp Tyr Phe	Pro		
145	150	155	160		
Glu Pro Val Thr Val	Ser Trp Asn Ser Gly Ala	Leu Thr Ser Gly	Val		
	165	170	175		
His Thr Phe Pro Ala	Val Leu Gln Ser Ser	Gly Leu Tyr Ser	Leu Ser		
	180	185	190		
Ser Val Val Thr Val	Pro Ser Ser Ser	Leu Gly Thr Gln	Thr Tyr Ile		
	195	200	205		
Cys Asn Val Asn His	Lys Pro Ser Asn Thr	Lys Val Asp Lys	Lys Val		
	210	215	220		
Glu Pro Lys Ser Glu	Phe				
225	230				

<210> 152
 <211> 222
 <212> PRT
 <213> Homo sapiens

<400> 152	
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	
1	5
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	
	20
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
	35
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val	
	50
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65	70
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
	85
Ala Arg Tyr Gly Ala Tyr Phe Gly Leu Asp Tyr Trp Gly Gln Gly Thr	
	100
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro	
	115
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly	
	130
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn	
145	150
	155
	160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 165 170 175
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 180 185 190
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 195 200 205
 Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 153

<211> 225

<212> PRT

<213> Homo sapiens

<400> 153

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
 20 25 30
 Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
 35 40 45
 Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
 50 55 60
 Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
 65 70 75 80
 Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
 85 90 95
 Tyr Tyr Cys Ala Arg Gly Tyr Ala Asp Ile Ser Phe Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 154

<211> 220

<212> PRT

<213> Homo sapiens

<400> 154

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Tyr Leu Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125
 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190
 Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205
 Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 155

<211> 229

<212> PRT

<213> Homo sapiens

<400> 155

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Trp Ser Asp Gln Ser Tyr His Tyr Tyr Trp His Pro Tyr Phe

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<210> 156
<211> 220
<212> PRT
<213> Homo sapiens
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<400> 156																
Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
1				5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
			20					25					30			
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
Ser	Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	
	50					55					60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	
65					70				75						80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
			85						90				95			
Ala	Arg	Leu	Ile	Gly	Tyr	Phe	Asp	Leu	Trp	Gly	Gln	Gly	Thr	Leu	Val	
			100					105					110			
Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	
		115					120					125				
Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	
	130					135					140					
Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	
145					150					155					160	
Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	
				165					170					175		
Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	
			180					185					190			
Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	
	195						200					205				

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 157
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 157
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Leu Thr Asn Tyr Phe Asp Ser Ile Tyr Tyr Asp His Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 158
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 158
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Leu Val Gly Gly Gly Tyr Asp Leu Met Phe Asp Ser Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 159

<211> 226

<212> PRT

<213> Homo sapiens

<400> 159

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Val Thr Tyr Gly Tyr Asp Asp Tyr His Phe Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125
 Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr

130 135 140
 Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160
 Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175
 Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190
 Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
 195 200 205
 His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
 210 215 220
 Glu Phe
 225

<210> 160
 <211> 219
 <212> PRT
 <213> Homo sapiens

<400> 160
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110
 Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
 115 120 125
 Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 130 135 140
 Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 145 150 155 160
 Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 165 170 175
 Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
 180 185 190
 Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 195 200 205
 Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215

<210> 161

<211> 231
 <212> PRT
 <213> Homo sapiens

<400> 161
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Ile Gly Tyr Thr Asn Val Met Asp Ile Arg Pro Gly Phe
 100 105 110
 Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
 115 120 125
 Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
 130 135 140
 Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
 145 150 155 160
 Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
 165 170 175
 Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
 180 185 190
 Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
 195 200 205
 Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
 210 215 220
 Val Glu Pro Lys Ser Glu Phe
 225 230

<210> 162
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 162
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Phe Arg Ala Tyr Gly Asp Asp Phe Tyr Phe Asp Val Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 163

<211> 228

<212> PRT

<213> Homo sapiens

<400> 163

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ile Met Trp Ser Asp Tyr Gly Gln Leu Val Lys Gly Gly Asp
 100 105 110
 Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
 115 120 125
 Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
 130 135 140
 Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
 145 150 155 160
 Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr

165 170 175
 Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
 180 185 190
 Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
 195 200 205
 Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
 210 215 220
 Lys Ser Glu Phe
 225

<210> 164
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 164
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Tyr Val Thr Asp Thr Ala Tyr Phe Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 165
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 165

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1          5          10          15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
          20          25          30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
          35          40          45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
          50          55          60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
          65          70          75          80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
          85          90          95
Ala Arg His Asp Phe Asp Gly Ser Ile Phe Met Asp Phe Trp Gly Gln
          100          105          110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
          115          120          125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
          130          135          140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
          145          150          155          160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
          165          170          175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
          180          185          190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
          195          200          205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
          210          215          220

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<210> 166

<211> 225

<212> PRT

<213> Homo sapiens .

<400> 166

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1          5          10          15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
          20          25          30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
          35          40          45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
          50          55          60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
          65          70          75          80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
          85          90          95
Ala Arg Tyr Ala Gly His Gln Tyr Glu Phe Phe Phe Asp Phe Trp Gly
          100          105          110

```

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 167

<211> 224

<212> PRT

<213> Homo sapiens

<400> 167

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Leu Tyr Ala Asp Ala Asp Ile Tyr Phe Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe

210 215 220

<210> 168
 <211> 222
 <212> PRT
 <213> Homo sapiens

<400> 168
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Lys Tyr Val Gly Ser Glu Asp Val Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 130 135 140
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 145 150 155 160
 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 165 170 175
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 180 185 190
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 195 200 205
 Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 169
 <211> 222
 <212> PRT
 <213> Homo sapiens

<400> 169
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

```

      50              55              60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65              70              75              80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
      85              90              95
Ala Arg Tyr Arg Tyr Pro His Met Phe Asp Phe Trp Gly Gln Gly Thr
      100              105              110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
      115              120              125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
      130              135              140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145              150              155              160
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
      165              170              175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
      180              185              190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
      195              200              205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
      210              215              220

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<210> 170

<211> 224

<212> PRT

<213> Homo sapiens

<400> 170

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1      5      10      15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
      20      25      30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
      35      40      45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
      50      55      60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65              70              75              80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
      85              90              95
Ala Arg Leu Phe Ala Gly Leu Glu Leu Tyr Phe Asp Tyr Trp Gly Gln
      100              105              110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
      115              120              125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
      130              135              140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145              150              155              160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165              170              175

```

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 171
 <211> 221
 <212> PRT
 <213> Homo sapiens

<400> 171
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Gly Gly Phe Phe Asn Met Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 115 120 125
 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140
 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160
 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 165 170 175
 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190
 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205
 Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 172
 <211> 223
 <212> PRT
 <213> Homo sapiens

<400> 172
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

```

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
      20      25      30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35      40      45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
      50      55      60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
      65      70      75      80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
      85      90      95
Ala Arg Gly Tyr Ile Pro Tyr His Leu Phe Asp Tyr Trp Gly Gln Gly
      100      105      110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
      115      120      125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
      130      135      140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
      145      150      155      160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
      165      170      175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
      180      185      190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
      195      200      205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
      210      215      220

```

<210> 173

<211> 225

<212> PRT

<213> Homo sapiens

<400> 173

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
      1      5      10      15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
      20      25      30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
      35      40      45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
      50      55      60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
      65      70      75      80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
      85      90      95
Ala Arg Tyr Tyr Gly Phe Glu Tyr Asp Leu Leu Phe Asp Asn Trp Gly
      100      105      110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
      115      120      125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala

```

130 135 140
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 210 215 220
 Phe
 225

<210> 174
 <211> 221
 <212> PRT
 <213> Homo sapiens

<400> 174
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ile Thr Tyr Ile Gly Tyr Asp Phe Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 115 120 125
 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140
 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160
 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 165 170 175
 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190
 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205
 Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215 220

<210> 175

<211> 220
 <212> PRT
 <213> Homo sapiens

<400> 175

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1          5          10          15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
          20          25          30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
          35          40          45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
          50          55          60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65          70          75          80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
          85          90          95
Ala Arg Gln Glu Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
          100          105          110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
          115          120          125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
          130          135          140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145          150          155          160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
          165          170          175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
          180          185          190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
          195          200          205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
          210          215          220

```

<210> 176
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 176

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1          5          10          15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
          20          25          30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
          35          40          45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
          50          55          60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65          70          75          80

```

```

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
      85      90      95
Ala Arg Leu Tyr Pro Glu Asp Leu Ile Tyr Phe Asp Tyr Trp Gly Gln
      100      105      110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
      115      120      125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
      130      135      140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145      150      155      160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
      165      170      175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
      180      185      190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
      195      200      205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
210      215      220

```

<210> 177

<211> 231

<212> PRT

<213> Homo sapiens

<400> 177

```

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1      5      10      15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
      20      25      30
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
      35      40      45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50      55      60
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65      70      75      80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
      85      90      95
Tyr Tyr Cys Ala Arg Trp Met Thr Pro Pro Gly His Tyr Tyr Gly Tyr
      100      105      110
Thr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
      115      120      125
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
130      135      140
Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
145      150      155      160
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
      165      170      175
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
      180      185      190
Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr

```

	195		200		205
Ile	Cys Asn Val Asn His	Lys Pro Ser Asn Thr	Lys Val Asp Lys Lys		
210		215	220		
Val Glu Pro Lys Ser	Glu Phe				
225	230				

<210> 178
 <211> 225
 <212> PRT
 <213> Homo sapiens

<400> 178

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
1				5					10					15	
Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Ser	Tyr
			20					25					30		
Trp	Ile	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Ile	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Thr	Arg	Tyr	Ser	Pro	Ser	Phe
	50					55					60				
Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Leu	Arg	Val	His	Asp	Tyr	Ala	Met	Tyr	Phe	Asp	Leu	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
		115					120					125			
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala
	130					135					140				
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
145					150					155					160
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
				165					170					175	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
			180					185					190		
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
		195					200					205			
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Glu
	210					215					220				
Phe															
225															

<210> 179
 <211> 226
 <212> PRT
 <213> Homo sapiens

<400> 179

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----


```

      1           5           10           15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
      20           25           30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
      35           40           45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
      50           55           60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
      65           70           75           80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
      85           90           95
Ala Arg Phe Val Ser Tyr Asn Gly Ser Val Pro Tyr Phe Asp Tyr Trp
      100          105          110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
      115          120          125
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
      130          135          140
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
      145          150          155          160
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
      165          170          175
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
      180          185          190
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
      195          200          205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
      210          215          220
Glu Phe
225

```

<210> 180

<211> 224

<212> PRT

<213> Homo sapiens

<400> 180

```

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
      1           5           10           15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
      20           25           30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
      35           40           45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
      50           55           60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
      65           70           75           80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
      85           90           95
Ala Arg Ile Ile Gly Asp Tyr Val Ile Phe Phe Asp Val Trp Gly Gln
      100          105          110

```

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
		115					120					125			
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
		130					135				140				
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
145					150					155					160
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
				165					170					175	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
			180					185					190		
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
		195					200					205			
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Glu	Phe
		210				215					220				

<210> 181

<211> 224

<212> PRT

<213> Homo sapiens

<400> 181

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
1			5						10				15		
Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Ser	Tyr
		20					25					30			
Trp	Ile	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Ile	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Thr	Arg	Tyr	Ser	Pro	Ser	Phe
50						55				60					
Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
			85						90				95		
Ala	Arg	Leu	Phe	Thr	Tyr	Pro	Phe	Leu	Tyr	Phe	Asp	Val	Trp	Gly	Gln
		100						105					110		
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<210> 276

<211> 669
 <212> DNA
 <213> Homo sapiens

<400> 276
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 gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
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 tattgggctg tttatcctta ttttgatttt tggggccaag gcaccctggt gacggttagc 360
 tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc 420
 ggcggcacgg ctgccctggg ctgccctggt aaagattatt tcccggaaac agtcaccgtg 480
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 agcgccctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag 600
 acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
 ccgaaaagc 669

<210> 277
 <211> 666
 <212> DNA
 <213> Homo sapiens

<400> 277
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 tggaacagcg gggcgctgac cagcggcgtg catacctttc cggcggtgct gcaaagcagc 540
 ggctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc 600
 tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaaccg 660
 aaaagc 666

<210> 278
 <211> 654
 <212> DNA
 <213> Homo sapiens

<400> 278
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 cctgggcagg gtctcgagt gatgggcggc attattccga tttttggcac ggcgaactac 180
 gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
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ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	ctcagaccta	tatttgcaac	600
gtgaaccata	aaccgagcaa	caccaaagtg	gataaaaaag	tggaaccgaa	aagc	654

<210> 279

<211> 666

<212> DNA

<213> Homo sapiens

<400> 279

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cctgggaagg	gtctcgagtg	ggtgagcgcg	attagcggta	gcggcggcag	cacctattat	180
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tggaacagcg	gggcgctgac	cagcggcgtg	catacctttc	cggcgggtgct	gcaaagcagc	540
ggcctgtata	gcctgagcag	cgttgtgacc	gtgccgagca	gcagcttagg	cactcagacc	600
tatatttgca	acgtgaacca	taaaccgagc	aacaccaaag	tgataaaaaa	agtggaaaccg	660
aaaagc						666

<210> 280

<211> 684

<212> DNA

<213> Homo sapiens

<400> 280

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cctgggcagg	gtctcgagtg	gatgggctgg	attaaccgga	atagcggcgg	cacgaactac	180
gcgcagaagt	ttcagggccg	ggtgaccatg	acccgtgata	ccagcattag	caccgcgtat	240
atggaactga	gcagcctgcg	tagcgaagat	acggccgtgt	attattgcgc	gcgtcttgtt	300
ggatttggtg	gttataagcc	tgatgagctt	ctttattttg	atgtttgggg	ccaaggcacc	360
ctggtgacgg	ttagctcagc	gtcgaccaa	ggtccaagcg	tgtttccgct	ggctccgagc	420
agcaaaaagca	ccagcggcgg	cacggctgcc	ctgggctgcc	tggttaaaga	ttattttcccg	480
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gcggtgctgc	aaagcagcgg	cctgtatagc	ctgagcagcg	ttgtgaccgt	gccgagcagc	600
agcttaggca	ctcagaccta	tatttgcaac	gtgaaccata	aaccgagcaa	caccaaagtg	660
gataaaaaag	tggaaccgaa	aagc				684

<210> 281

<211> 660

<212> DNA

<213> Homo sapiens

<400> 281

caggtgcaat	tgggtgaaag	cggcggcggc	ctggtgcaac	cgggcggcag	cctgcgtctg	60
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agctgcgcgg	cctccggatt	taccttttagc	agctatgcga	tgagctgggt	gcgccaagcc	120
cctgggaagg	gtctcgagtg	ggtgagcgcg	attagcggta	gcggcggcag	cacctattat	180
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tatagcctga	gcagcgttgt	gaccgtgccg	agcagcagct	taggcactca	gacctatatt	600
tgcaacgtga	accataaacc	gagcaacacc	aaagtggata	aaaaagtgga	accgaaaagc	660

<210> 282

<211> 669

<212> DNA

<213> Homo sapiens

<400> 282

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cagtctcctg	ggcgtggcct	cgagtggctg	ggccgtacct	attatcgtag	caaatggtat	180
aacgattatg	cggtgagcgt	gaaaagccgg	attaccatca	acccggatag	ttcgaaaaac	240
cagtttagcc	tgcaactgaa	cagcgtgacc	ccggaagata	cggccgtgta	ttattgcgcg	300
cggtggttatg	ctgatatttc	ttttgattat	tggggccaa	gcaccctggt	gacggttagc	360
tcagcgtcga	ccaaagggtcc	aagcgtgttt	ccgctggctc	cgagcagcaa	aagcaccagc	420
ggcggcacgg	ctgccctggg	ctgcctgggt	aaagattatt	tcccgggaacc	agtcaccgtg	480
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agcggcctgt	atagcctgag	cagcgttgtg	accgtgccga	gcagcagctt	aggcactcag	600
acctatattt	gcaacgtgaa	ccataaacgg	agcaacacca	aagtggataa	aaaagtggaa	660
ccgaaaagc						669

<210> 283

<211> 654

<212> DNA

<213> Homo sapiens

<400> 283

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cctgggaagg	gtctcgagtg	ggtgagcgcg	attagcggta	gcggcggcag	cacctattat	180
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cttcttcttg	attattgggg	ccaaggcacc	ctggtgacgg	ttagctcagc	gtcgaccaa	360
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ctgggctgcc	tggttaaaga	ttatttcccg	gaaccagtca	ccgtgagctg	gaacagcggg	480
gcgctgacca	gcggcgtgca	tacctttccg	gcgggtgctgc	aaagcagcgg	cctgtatagc	540
ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	ctcagacct	tatttgcaac	600
gtgaaccata	aaccgagcaa	caccaaagtg	gataaaaaag	tggaaccgaa	aagc	654

<210> 284

<211> 681

<212> DNA

<213> Homo sapiens

<400> 284

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cctgggcagg	gtctcgagtg	gatgggcggc	attattccga	tttttggcac	ggcgaactac	180
gcgcagaagt	ttcagggccg	ggtgaccatt	accgcggatg	aaagcaccag	caccgcgtat	240
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gatcagtcct	atcattatta	ttggcatcct	tattttgatg	tttggggcca	aggcaccctg	360
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ccagtcaccg	tgagctggaa	cagcggggcg	ctgaccagcg	gcgtgcatac	ctttccggcg	540
gtgctgcaaa	gcagcggcct	gtatagcctg	agcagcgttg	tgaccgtgcc	gagcagcagc	600
ttaggcactc	agacatatat	ttgcaacgtg	aaccataaac	cgagcaaac	caaagtggat	660
aaaaaagtgg	aaccgaaaag	c				681

<210> 285

<211> 654

<212> DNA

<213> Homo sapiens

<400> 285

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cctgggaagg	gtctcgagtg	ggtgagcgcg	attagcggtg	gcggcggcag	cacctattat	180
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ctgcaaatga	acagcctgcg	tgcggaagat	acggccgtgt	attattgcgc	gcgtcttatt	300
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ggtccaagcg	tgtttccgct	ggctccgagc	agcaaaagca	ccagcggcgg	cacggctgcc	420
ctgggctgcc	tgggttaaaga	ttatttcccg	gaaccagtca	ccgtgagctg	gaacagcggg	480
gcgctgacca	gcggcgtgca	tacctttccg	gcgggtgctgc	aaagcagcgg	cctgtatagc	540
ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	ctcagacctg	tatttgcaac	600
gtgaaccata	aaccgagcaa	caccaaagtg	gataaaaaag	tggaaccgaa	aagc	654

<210> 286

<211> 669

<212> DNA

<213> Homo sapiens

<400> 286

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cctgggaagg	gtctcgagtg	gatgggcatt	atttatccgg	gcgatagcga	taccggttat	180
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ggcggcacgg	ctgcccctggg	ctgcctgggt	aaagattatt	tcccgggaacc	agtcaccgtg	480
agctggaaca	gcggggcgct	gaccagcggc	gtgcatacct	ttccggcggt	gctgcaaagc	540

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agcggcctgt atagcctgag cagcgtttgtg accgtgccga gcagcagctt aggcaactcag      600
acctatatatt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa      660
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<210> 287

<211> 669

<212> DNA

<213> Homo sapiens

<400> 287

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tctccgagct ttcagggccca ggtgaccatt agcgcggata aaagcattag caccgcgtat     240
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acctatatatt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa     660
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<210> 288

<211> 672

<212> DNA

<213> Homo sapiens

<400> 288

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cagacctata tttgcaacgt gaaccataaa ccgagcaaca ccaaagtgga taaaaaagtg     660
gaaccgaaaa gc                                         672

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<210> 289

<211> 651

<212> DNA

<213> Homo sapiens

<400> 289

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agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc     120

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cctgggcagg	gtctcgagt	gatgggcggc	attattccga	tttttggcac	ggcgaactac	180
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agcagcylly	tgaccgtgcc	gagcagcagc	ttaggcactc	agacctatat	ttgcaacgtg	600
aaccataaac	cgagcaaacac	caaagtggat	aaaaaagtgg	aaccgaaaag	c	651

<210> 290

<211> 687

<212> DNA

<213> Homo sapiens

<400> 290

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<210> 291

<211> 669

<212> DNA

<213> Homo sapiens

<400> 291

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tctccgagct	ttcagggcca	ggtgaccatt	agcgcggata	aaagcattag	caccgcgtat	240
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acctatattt	gcaacgtgaa	ccataaaccg	agcaaacacca	aagtggataa	aaaagtggaa	660
ccgaaaagc						669

<210> 292

<211> 678

<212> DNA

<213> Homo sapiens

<400> 292

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ctgcaaagca	gcggcctgta	tagcctgagc	agcgttgtga	ccgtgccgag	cagcagctta	600
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aaagtggaac	cgaaaagc					678

<210> 293

<211> 666

<212> DNA

<213> Homo sapiens

<400> 293

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ggcctgtata	gcctgagcag	cggtgtgacc	gtgccgagca	gcagcttagg	cactcagacc	600
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<210> 294

<211> 666

<212> DNA

<213> Homo sapiens

<400> 294

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ggcctgtata	gcctgagcag	cggtgtgacc	gtgccgagca	gcagcttagg	cactcagacc	600
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<210> 295

<211> 669

<212> DNA

<213> Homo sapiens

<400> 295

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agcggcctgt	atagcctgag	cagcgttgtg	accgtgccga	gcagcagctt	aggcactcag	600
acctatattt	gcaacgtgaa	ccataaacgg	agcaacacca	aagtggataa	aaaagtggaa	660
ccgaaaagc						669

<210> 296

<211> 614

<212> DNA

<213> Homo sapiens

<400> 296

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ccggttatc	tccgagcttt	cagggccagg	tgaccattag	cgcgataaa	agcattagca	180
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aaagcagcgg	cctgtatagc	ctgagcagcg	ttgtgaccgt	gccgagcagc	agcttaggca	540
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<210> 297

<211> 660

<212> DNA

<213> Homo sapiens

<400> 297

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tatagcctga	gcagcgttgt	gaccgtgccg	agcagcagct	taggcactca	gacctatatt	600
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<210> 298

<211> 660

<212> DNA

<213> Homo sapiens

<400> 298

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tctccgagct	ttcagggcca	ggtgaccatt	agcgcggata	aaagcattag	caccgcgtat	240
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tatcctcata	tgtttgattt	ttggggccaa	ggcaccctgg	tgacggttag	ctcagcgtcg	360
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<210> 299

<211> 666

<212> DNA

<213> Homo sapiens

<400> 299

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gctggtcctg	agctttattt	tgattattgg	ggccaaggca	ccctggtgac	ggttagctca	360
gcgtcgacca	aaggtccaag	cgtgtttccg	ctggctccga	gcagcaaaag	caccagcggc	420
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ggcctgtata	gcctgagcag	cgttgtgacc	gtgccgagca	gcagcttagg	cactcagacc	600
tatatttgca	acgtgaacca	taaaccgagc	aacaccaaag	tggataaaaa	agtggaaccg	660
aaaagc						666

<210> 300

<211> 657

<212> DNA

<213> Homo sapiens

<400> 300

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ggggcgctga	ccagcggcgt	gcataccttt	ccggcgggtc	tgcaaacgag	cggcctgtat	540
agcctgagca	gcgttgtgac	cgtgccgagc	agcagcttag	gcactcagac	ctatatattg	600
aacgtgaacc	ataaaccgag	caacaccaaa	gtggataaaa	aagtggaacc	gaaaagc	657

<210> 301

<211> 663

<212> DNA

<213> Homo sapiens

<400> 301

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ctgtatagcc	tgagcagcgt	tgtgaccgtg	ccgagcagca	gcttaggcac	tcagacctat	600
atttgcaacg	tgaaccataa	accagcaaac	accaaagtgg	ataaaaaagt	ggaaccgaaa	660
agc						663

<210> 302

<211> 669

<212> DNA

<213> Homo sapiens

<400> 302

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agcggcctgt	atagcctgag	cagcgttgtg	accgtgccga	gcagcagctt	aggcactcag	600

acctatatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660
ccgaaaagc 669

<210> 303

<211> 657

<212> DNA

<213> Homo sapiens

<400> 303

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aacgtgaacc	ataaaccgag	caacaccaaa	gtggataaaa	aagtggaacc	gaaaagc	657

<210> 304

<211> 654

<212> DNA

<213> Homo sapiens

<400> 304

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<210> 305

<211> 666

<212> DNA

<213> Homo sapiens

<400> 305

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<210> 306

<211> 687

<212> DNA

<213> Homo sapiens

<400> 306

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<210> 307

<211> 669

<212> DNA

<213> Homo sapiens

<400> 307

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<210> 308

<211> 672

<212> DNA

<213> Homo sapiens

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<210> 309
<211> 666
<212> DNA
<213> Homo sapiens

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<400> 309
caggtgcaat tggttcagag cggcgcgga gtgaaaaaac cgggcgaaag cctgaaaatt    60
agctgcaaag gtcccgata ttccctttacg agctattgga ttggctgggt gcgccagatg    120
cctgggaagg gtctcgagt gatgggcatt atttatccgg gcgatagcga taccggttat    180
tctccgagct ttcagggcca ggtgaccatt agcgcgata aaagcattag caccgcgtat    240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtattatt    300
ggtgattatg ttattttttt tgatgttttg ggccaaggca ccctggtgac ggttagctca    360
gcgtcgacca aagggtccaag cgtgtttccg ctggctccga gcagcaaaaag caccagcggc    420
ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc    480
tggaacagcg gggcgctgac cagcggcgtg catacctttc cggcggtgct gcaaagcagc    540
ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc    600
tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtgaaccg    660
aaaagc

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<210> 310
<211> 609
<212> DNA
<213> Homo sapiens

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<400> 310
attagctgca aaggttccgg atattccttt acgagctatt ggattggctg ggtgcgccag    60
atgcctggga agggctctga gtggatgggc attattttatc cgggcgatag cgatacccg    120
tattctccga gctttcaggg ccaggtgacc attagcgcgg ataaaagcat tagcaccgcg    180
tatcttcaat ggagcagcct gaaagcgagc gatacggcca tgtattattg cgcgcgtctt    240
tttacttata cttttcttta ttttgatgtt tggggccaag gcaccctggt gacggttagc    300
tcagcgtcga ccaaaggctc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc    360
ggcggcacgg ctgccctggg ctgccctggt aaagattatt tcccggaacc agtcaccgtg    420
agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc    480
agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag    540
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa    600

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ccgaaaaagc

609

<210> 311

<211> 666

<212> DNA

<213> Homo sapiens

<400> 311

caggtgcaat	tggttcagag	cggcgcgga	gtgaaaaaac	cgggcgaaag	cctgaaaatt	60
agctgcaaaag	gttccggata	ttcctttacg	agctattgga	ttggctgggt	gcgccagatg	120
cctgggaagg	gtctcgagt	gatgggcatt	atztatccgg	gcgatagcga	taccggttat	180
tctccgagct	ttcaggggcca	ggtgaccatt	agcgcgata	aaagcattag	caccgcgtat	240
cttcaatgga	gcagcctgaa	agcgagcgat	acggccatgt	attattgcgc	gcgtattctt	300
actggtcacg	ttcttctttt	tgattattgg	ggccaaggca	ccctggtgac	ggttagctca	360
gcgtcgacca	aaggtccaag	cgtgtttccg	ctggctccga	gcagcaaaag	caccagcggc	420
ggcacggctg	ccctgggctg	cctgggttaa	gattatttcc	cgaaccagt	caccgtgagc	480
tggaacagcg	ggcgctgac	cagcgcgctg	cataccttcc	cggcggtgct	gcaaagcagc	540
ggcctgtata	gcctgagcag	cgttgtgacc	gtgccgagca	gcagcttagg	cactcagacc	600
tatatttgca	acgtgaacca	taaaccgagc	aacaccaaag	tggataaaaa	agtggaaccg	660
aaaagc						666

<210> 312

<211> 645

<212> DNA

<213> Homo sapiens

<400> 312

gatatcgcaac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actatcagca	gtttactgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggg	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggco		645

<210> 313

<211> 645

<212> DNA

<213> Homo sapiens

<400> 313

gatatcgcaac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttaagac	ttatcttgtg	300

tttggcgggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 314

<211> 645

<212> DNA

<213> Homo sapiens

<400> 314

gatatcgac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttcttcg	tttttctgtg	300
tttggcgggc	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 315

<211> 638

<212> DNA

<213> Homo sapiens

<400> 315

gatatcgac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttattaa	tgttattgtg	300
tttggcgggc	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgac			638

<210> 316

<211> 645

<212> DNA

<213> Homo sapiens

<400> 316

gatatcgac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
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tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttgttcg	ttttatggtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		645

<210> 317

<211> 638

<212> DNA

<213> Homo sapiens

<400> 317

gatatacgac	tgaccagacc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acttttataa	gtttaatgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgac			638

<210> 318

<211> 638

<212> DNA

<213> Homo sapiens

<400> 318

gatatacgac	tgaccagacc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	actttcgtcg	tttttctgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccgtt	gcgccgac			638

<210> 319

<211> 642

<212> DNA

<213> Homo sapiens

<400> 319

gatatcgtgc	tgaccagcc	gccttcagt	agtggcgac	caggtcagcg	tgtgaccatc	60
tcgtgtagcg	gcagcagcag	caacattggc	agcaactatg	tgagctggta	ccagcagttg	120
cccgggacgg	cgccgaaact	gctgatttat	gataacaacc	agcgtccctc	aggcgtgccg	180
gacggtttta	gcggatccaa	aagcggcacc	agcgcgagcc	ttgcgattac	gggcctgcaa	240
agcgaagacg	aagcggatta	ttattgccag	agccgtgact	ttaatcgtgg	tcctgtgttt	300
ggcggcgcca	cgaagttaac	cgttcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgccga	gcagcgaaga	attgcaggcg	aacaaagcga	ccctgggtgtg	cctgattagc	420
gactttttatc	cgggagccgt	gacagtggcc	tgggaaggcag	atagcagccc	cgtcaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgagcctga	cgccctgagca	gtggaagtcc	cacagaagct	acagctgcc	ggtcacgcat	600
gaggggagca	ccgtggaaaa	aaccgttgcg	ccgactgagg	cc		642

<210> 320

<211> 639

<212> DNA

<213> Homo sapiens

<400> 320

gatatcgtgc	tgaccagcc	gccttcagt	agtggcgac	caggtcagcg	tgtgaccatc	60
tcgtgtagcg	gcagcagcag	caacattggc	agcaactatg	tgagctggta	ccagcagttg	120
cccgggacgg	cgccgaaact	gctgatttat	gataacaacc	agcgtccctc	aggcgtgccg	180
gacggtttta	gcggatccaa	aagcggcacc	agcgcgagcc	ttgcgattac	gggcctgcaa	240
agcgaagacg	aagcggatta	ttattgccag	agctatgacc	agcgttaagt	ggtgtttggc	300
ggcggcacga	agttaaccgt	tcttgccag	ccgaaagccg	caccgagtgt	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tggtgtgcct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcggga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgagcg	ctgagcagtg	gaagtccac	agaagctaca	gctgccaggt	cacgcatgag	600
gggagcaccg	tggaaaaaac	cgttgccg	actgagggc			639

<210> 321

<211> 672

<212> DNA

<213> Homo sapiens

<400> 321

gatatcgtgc	tgaccagag	cccggcgacc	ctgagcctgt	ctccgggcca	acgtgcgacc	60
ctgagctgca	gagcgagcca	gagcgtgagc	agcagctatc	tggcgtggta	ccagcagaaa	120
ccaggtcaag	caccgcgtct	attaatttat	ggcgcgagca	gccgtgcaac	tggggtcccg	180
gcgcgtttta	gcggctctgg	atccggcacg	gattttaccc	tgaccattag	cagcctggaa	240
cctgaagact	ttgcgactta	ttattgccag	cagctttatg	gtacttctgt	tacctttggc	300
cagggtacga	aagttgaaat	taaacgtacg	gtggctgctc	cgagcgtgtt	tatttttccg	360
ccgagcgatg	aacaactgaa	aagcggcacg	gcgagcgtgg	tgtgcctgct	gaacaacttt	420
tatccgcgtg	aagcgaaggt	tcagtggaaa	gtagacaacg	cgctgcaaag	cggcaacagc	480
caggaaaagcg	tgaccgaaca	ggatagcaaa	gatagcacct	attctctgag	cagcaccctg	540
accctgagca	aagcggatta	tgaaaaacat	aaagtgtatg	cgtgcgaagt	gacccatcaa	600
ggtctgagca	gcccgggtgac	taaatctttt	aatcgtggcg	aggcctgata	agcatgcgta	660

ggagaaaata aa

672

<210> 322

<211> 642

<212> DNA

<213> Homo sapiens

<400> 322

gatatcgtgc	tgacccagcc	gccttcagtg	agtggcgcac	caggtcagcg	tgtgaccatc	60
tcgtgtagcg	gcagcagcag	caacattggc	agcaactatg	tgagctggta	ccagcagttg	120
cccgggacgg	cgccgaaact	gctgatttat	gataacaacc	agcgtccctc	aggcgtgccg	180
gatcggttta	gcggatccaa	aagcggcacc	agcgcgagcc	ttgcgattac	gggcctgcaa	240
agcgaagacg	aagcggatta	ttattgccag	agctatgacg	gttttaagac	tcatgtgttt	300
ggcggcgcca	cgaagttaac	cgttcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgccga	gcagcgaaga	attgcaggcg	aacaaagcga	ccctggtgtg	cctgattagc	420
gactttttatc	cgggagccgt	gacagtggcc	tggaaggcag	atagcagccc	cgtcaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgagcctga	cgctgagca	gtggaagtcc	cacagaagct	acagctgcca	ggtcacgcat	600
gaggggagca	ccgtggaaaa	aaccgttgcc	ccgactgagg	cc		642

<210> 323

<211> 633

<212> DNA

<213> Homo sapiens

<400> 323

gatatcgaac	tgacccagcc	gccttcagtg	agcgttgcac	caggtcagac	cgcgcgatc	60
tcgtgtagcg	gcgatgcgct	gggcgataaa	tacgcgagct	ggtaccagca	gaaacccggg	120
caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcggaa	240
gacgaagcgg	attattattg	ccagagctat	gactattctc	ttcttggtgt	tggcggcggc	300
acgaagttaa	ccgttcttgg	ccagccgaaa	gccgcaccga	gtgtgacgct	gtttccgccg	360
agcagcgaag	aattgcaggc	gaacaaagcg	accctggtgt	gcctgattag	cgacttttat	420
ccgggagccg	tgacagtggc	ctggaaggca	gatagcagcc	ccgtcaaggc	gggagtggag	480
accaccacac	cctccaaaca	aagcaacaac	aagtacgcgg	ccagcagcta	tctgagcctg	540
acgcctgagc	agtggaagtc	ccacagaagc	tacagctgcc	aggtcacgca	tgaggggagc	600
accgtggaaa	aaaccgttgc	gccgactgag	gcc			633

<210> 324

<211> 633

<212> DNA

<213> Homo sapiens

<400> 324

gatatcgaac	tgacccagcc	gccttcagtg	agcgttgcac	caggtcagac	cgcgcgatc	60
tcgtgtagcg	gcgatgcgct	gggcgataaa	tacgcgagct	ggtaccagca	gaaacccggg	120
caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcggaa	240
gacgaagcgg	attattattg	ccagagctat	gactttaatt	ttcatgtgtt	tggcggcggc	300
acgaagttaa	ccgttcttgg	ccagccgaaa	gccgcaccga	gtgtgacgct	gtttccgccg	360

agcagcgaag	aattgcaggc	gaacaaagcg	accctggtgt	gcctgattag	cgacttttat	420
ccgggagccg	tgacagtggc	ctggaaggca	gatagcagcc	ccgtcaaggc	gggagtggag	480
accaccacac	cctccaaaca	aagcaacaac	aagtacgcgg	ccagcagcta	tctgagcctg	540
acgcctgagc	agtggaagtc	ccacagaagc	tacagctgcc	aggtcacgca	tgaggggagc	600
accgtggaaa	aaaccgttgc	gccgactgag	gcc			633

<210> 325

<211> 648

<212> DNA

<213> Homo sapiens

<400> 325

gatatcgcaac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acatgattgc	tcgttatcct	300
gtgtttggcg	gcggcacgaa	gttaaccgtt	cttggccagc	cgaaagccgc	accgagtgtg	360
acgctgtttc	cgccgagcag	cgaagaattg	caggcgaaca	aagcgaccct	ggtgtgcctg	420
attagcgact	tttatccggg	agccgtgaca	gtggcctgga	aggcagatag	cagccccgtc	480
aaggcgggag	tggagaccac	cacaccctcc	aaacaaagca	acaacaagta	cgcgccagc	540
agctatctga	gcctgacgcc	tgagcagtg	aagtcccaca	gaagctacag	ctgccaggtc	600
acgcatgagg	ggagcaccgt	ggaaaaaac	gttgccgcca	ctgaggcc		648

<210> 326

<211> 639

<212> DNA

<213> Homo sapiens

<400> 326

gatatcgaac	tgaccagcc	gccttcagtg	agcgttgcaac	caggtcagac	cgcgcgatc	60
tcgtgtagcg	gcgatgcgct	gggcgataaa	tacgcgagct	ggtaccagca	gaaaccggg	120
caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccgaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcggaa	240
gacgaagcgg	attattattg	ccagagctgg	gacattcatc	cttttgatgt	tgtgtttggc	300
ggcgccacga	agttaaccgt	tcttggccag	ccgaaagccg	caccgagtgt	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaa	aaagcgaccc	tggtgtgcct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcggga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagtg	gaagtccac	agaagctaca	gctgccaggt	cacgcatgag	600
gggagcaccg	tggaaaaaac	cggtgcgccg	actgaggcc			639

<210> 327

<211> 639

<212> DNA

<213> Homo sapiens

<400> 327

gatatcgctg	tgaccagcc	gccttcagtg	agtggcgcaac	caggtcagcg	tgtgaccatc	60
tcgtgtagcg	gcagcagcag	caacattggc	agcaactatg	tgagctggta	ccagcagttg	120

cccgggacgg	cgccgaaact	gctgatttat	gataacaacc	agcgtccctc	aggcgtgccg	180
gatcggtttta	gcggatccaa	aagcggcacc	agcgcgagcc	ttgcgattac	gggcctgcaa	240
agcgaagacg	aagcggatta	ttattgccag	agctgggacc	ttgagcctta	tgtgtttggc	300
ggcggcacga	agttaaccgt	tcttgccag	ccgaaagccg	caccgagtgt	gacgctgttt	360
ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tggtgtgcct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcggga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagtg	gaagtccac	agaagctaca	gctgccaggt	cacgcatgag	600
gggagcaccg	tggaaaaaac	cgttgccgcg	actgaggcc			639

<210> 328

<211> 645

<212> DNA

<213> Homo sapiens

<400> 328

gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgcgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcgggaag	acgaagcgga	ttattattgc	cagagctatg	acgttcttga	ttctgagggtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtgggaag	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaccggt	gcgccgactg	aggcc		645

<210> 329

<211> 648

<212> DNA

<213> Homo sapiens

<400> 329

gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgcgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccggt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcgggaag	acgaagcgga	ttattattgc	cagagctatg	acccttctca	tccttctaag	300
gtgtttggcg	gcggcacgaa	gttaaccggt	cttggccagc	cgaagccgcg	accgagtgtg	360
acgctgtttc	cgccgagcag	cgaagaattg	caggcgaaca	aagcgaccct	ggtgtgcctg	420
attagcgact	tttatccggg	agccgtgaca	gtggcctgga	aggcagatag	cagccccgtc	480
aaggcgggag	tggagaccac	cacaccctcc	aaacaaagca	acaacaagta	cgcgccagc	540
agctatctga	gcctgacgcc	tgagcagtg	aagtcccaca	gaagctacag	ctgccaggtc	600
acgcatgagg	ggagcaccgt	ggaaaaaac	gttgccgcga	ctgaggcc		648

<210> 330

<211> 642

<212> DNA

<213> Homo sapiens

<400> 330
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 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctccaggcgtg 180
 agcaaccggt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcgga ttattattgc cagagctatg acgatatgca gtttgtgttt 300
 ggcggcggca cgaagttaac cgttcttggc cagccgaaag ccgcaccgag tgtgacgctg 360
 tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctgggtgtg cctgattagc 420
 gacttttatt cgggagccgt gacagtggcc tgggaagcag atagcagccc cgtcaaggcg 480
 ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
 ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgccca ggtcacgcat 600
 gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc 642

<210> 331
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 331
 gatatcgac tgaccagcc agcttcagt agcggctcac caggtcagag cattaccatc 60
 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctccaggcgtg 180
 agcaaccggt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcgga ttattattgc cagagctggg acattaatca tgctattgtg 300
 tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg 360
 ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgacctggt gtgcctgatt 420
 agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtaag 480
 gcgggagtg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540
 tatctgagcc tgacgcctga gcagtggaa tcccacagaa gctacagctg ccaagtacacg 600
 catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc 645

<210> 332
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 332
 gatatcgac tgaccagcc agcttcagt agcggctcac caggtcagag cattaccatc 60
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 catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctccaggcgtg 180
 agcaaccggt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcgga ttattattgc cagagctatg actattatga ttatgggtgtg 300
 tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg 360
 ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgacctggt gtgcctgatt 420
 agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtaag 480
 gcgggagtg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540
 tatctgagcc tgacgcctga gcagtggaa tcccacagaa gctacagctg ccaggtcacg 600
 catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc 645

<210> 333
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 333
 gatatcgtgc tgaccagag cccggcgacc ctgagcctgt ctccgggcca acgtgcgacc 60
 ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tggggtcccg 180
 gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcggttta ttattgccag caggctaattg attttcctat tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg gtggctgctc cgagcgtgtt tatttttccg 360
 ccgagcgatg aacaactgaa aagcggcacg gcgagcgtgg tgtgcctgct gaacaacttt 420
 tatccgcgtg aagcgaaggt tcagtggaaa gttagacaac cgctgcaaac cggcaacagc 480
 caggaaaagc tgacggaaca ggatagcaaa gatagcacct attctctgag cagcaccctg 540
 accctgagca aagcggatta tgaaaaacat aaagtgtatg cgtgcgaagt gacccatcaa 600
 ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcc 645

<210> 334
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 334
 gatatcgac tgaccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60
 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgcgcaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
 agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcgggaag acgaagcggg ttattattgc cagagctggg acaatcttaa gatgcctgtt 300
 gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg 360
 acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg 420
 attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 480
 aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc 540
 agctatctga gcctgacgac tgagcagtgg aagtcaccaca gaagctacag ctgccaggtc 600
 acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgaggcc 648

<210> 335
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 335
 gatatcgac tgaccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60
 tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag 120
 catcccggga aggcgcgcaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
 agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcgggaag acgaagcggg ttattattgc cagagctatg acgtttttcc tattaatcgt 300
 gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg 360
 acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg 420
 attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 480

aaggcgggag	tggagaccac	cacaccctcc	aaacaaagca	acaacaagta	cgcgccagc	540
agctatctga	gcctgacgcc	tgagcagtgg	aagtcccaca	gaagctacag	ctgccaggtc	600
acgcatgagg	ggagcaccgt	ggaaaaaacc	gttgcgccga	ctgaggcc		648

<210> 336
 <211> 639
 <212> DNA
 <213> Homo sapiens

<400> 336						
gatatcgac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagcgatc	tttattttcc	tgtgtttggc	300
ggcggcacga	agttaaccgt	tcttggccag	ccgaaagccg	caccgagtg	gacgctgtt	360
ccgcgagca	gcgaagaatt	gcaggcgaa	aaagcgaccc	tgggtgtgcct	gattagcgac	420
ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	caaggcgga	480
gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	cagctatctg	540
agcctgacgc	ctgagcagtg	gaagtccac	agaagctaca	gctgccaggt	cacgcatgag	600
gggagcaccg	tggaaaaaac	cggtgcgccg	actgaggcc			639

<210> 337
 <211> 642
 <212> DNA
 <213> Homo sapiens

<400> 337						
gatatcgac	tgaccagcc	agcttcagt	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcggtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagctatg	acgttactcc	tcgtgtgtt	300
ggcggcggca	cgaagttaac	cggtcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgcgga	gcagcgaaga	attgcaggcg	aacaaagcga	ccctgggtgtg	cctgattagc	420
gacttttatc	cgggagccgt	gacagtggcc	tgggaaggcag	atagcagccc	cgtaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacggggc	cagcagctat	540
ctgagcctga	cgctgagca	gtggaagtcc	cacagaagct	acagctgcca	ggcacgcac	600
gaggggagca	ccgtggaaaa	aaccgttgccg	ccgactgagg	cc		642

<210> 338
 <211> 636
 <212> DNA
 <213> Homo sapiens

<400> 338						
gatatcgaac	tgaccagcc	gccttcagt	agcgttgac	caggtcagac	cgcgcgatc	60
tcgtgtagcg	gcgatgcgct	ggcgataaa	tacgcgagct	ggtaccagca	gaaacccggg	120
caggcgccag	ttctgggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccgaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcggaa	240

gacgaagcgg	attattattg	ccagagccgt	gaccctgttg	gttttcctgt	gtttggcggc	300
ggcacgaagt	taaccgttct	tggccagccg	aaagccgcac	cgagtgtgac	gctgtttccg	360
ccgagcagcg	aagaattgca	ggcgaacaaa	gcgaccctgg	tgtgcctgat	tagcgacttt	420
tatccgggag	ccgtgacagt	ggcctggaag	gcagatagca	gccccgtcaa	ggcgggagtg	480
gagaccacca	caccctccaa	acaaagcaac	aacaagtacg	cggccagcag	ctatctgagc	540
ctgacgcctg	agcagtgga	gtcccacaga	agctacagct	gccaggtcac	gcatgagggg	600
agcaccgtgg	aaaaaacctg	tgcgccgact	gaggcc			636

<210> 339
 <211> 642
 <212> DNA
 <213> Homo sapiens

<400> 339						
gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgctg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcgggaag	acgaagcggg	ttattattgc	cagagctatg	acctttctcc	tcgtgtgttt	300
ggcggcggca	cgaagttaac	cgttcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgcgca	gcagcgaaga	attgcaggcg	aacaaagcga	ccctggtgtg	cctgattagc	420
gactttttatc	cgggagccgt	gacagtggcc	tggaaaggcag	atagcagccc	cgtaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgagcctga	cgctgagca	gtggaagtcc	cacagaagct	acagctgcc	ggcacgcat	600
gaggggagca	ccgtggaaaa	aaccgttgcg	ccgactgagg	cc		642

<210> 340
 <211> 648
 <212> DNA
 <213> Homo sapiens

<400> 340						
gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgctg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcgggaag	acgaagcggg	ttattattgc	cagagctatg	acttttctca	ttattttttt	300
gtgtttggcg	gcggcacgaa	gttaaccgtt	cttgccagc	cgaaagccgc	accgagtgtg	360
acgctgtttc	cgccgagcag	cgaagaattg	caggcgaaaca	aagcgaccct	ggtgtgcctg	420
attagcgact	tttatccggg	agccgtgaca	gtggcctgga	aggcagatag	cagccccgtc	480
aaggcgggag	tggagaccac	cacaccctcc	aaacaaagca	acaacaagta	cgcgccagc	540
agctatctga	gcctgacgcc	tgagcagtgg	aagtccaca	gaagctacag	ctgccaggtc	600
acgcatgagg	ggagcaccgt	ggaaaaaacc	gttgcccgca	ctgaggcc		648

<210> 341
 <211> 636
 <212> DNA
 <213> Homo sapiens

<400> 341

gatatcgaaac	tgaccagcc	gccttcagtg	agcgttgac	caggtcagac	cgcgcgatc	60
tcgtgtacg	gcgatgcgct	ggcgataaa	tacgcgagct	ggtaccagca	gaaacccggg	120
caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcgga	240
gacgaagcgg	attattattg	ccagagctat	gaccttcgtt	attctcatgt	gtttggcggc	300
ggcaggaagt	taaccgttct	tggccagccg	aaagccgcac	cgagtgtgac	gctgtttccg	360
ccgagcagcg	aagaattgca	ggcgaacaaa	gcgaccctgg	tgtgcctgat	tagcgacttt	420
tatccgggag	ccgtgacagt	ggcctggaag	gcagatagca	gccccgtcaa	ggcgggagtg	480
gagaccacca	caccctccaa	acaaagcaac	aacaagtacg	cggccagcag	ctatctgagc	540
ctgacgcctg	agcagtggaa	gtcccacaga	agctacagct	gccaggtcac	gcatgagggg	600
agcaccgtgg	aaaaaaccgt	tgcgccgact	gaggcc			636

<210> 342

<211> 642

<212> DNA

<213> Homo sapiens

<400> 342

gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgctg	180
agcaaccggt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcgggaag	acgaagcggg	ttattattgc	cagagctatg	accttcgtaa	tcgtgtgttt	300
ggcggcgcca	cgaagttaac	cggttcttggc	cagccgaaag	ccgcaccgag	tgtgacgctg	360
tttccgcgca	gcagcgaaga	attgcaggcg	aacaaagcga	ccctggtgtg	cctgattagc	420
gactttttatc	cgggagccgt	gacagtggcc	tgggaaggcag	atagcagccc	cgtaaggcg	480
ggagtggaga	ccaccacacc	ctccaaacaa	agcaacaaca	agtacggggc	cagcagctat	540
ctgagcctga	cgcttgagca	gtggaagtcc	cacagaagct	acagctgcc	ggtcacgcat	600
gaggggagca	ccgtggaaaa	aaccgttgcg	ccgactgagg	cc		642

<210> 343

<211> 645

<212> DNA

<213> Homo sapiens

<400> 343

gatatcgac	tgaccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacg	gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgctg	180
agcaaccggt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcgggaag	acgaagcggg	ttattattgc	cagagctatg	actttactta	tggttctgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccgggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaa	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
catgagggga	gcaccgtgga	aaaaaaccgtt	gcgccgactg	aggcc		645

<210> 344

<211> 645

<212> DNA

<213> Homo sapiens

<400> 344

gatatcgtgc	tgaccagag	cccggcgacc	ctgagcctgt	ctccgggcga	acgtgcgacc	60
ctgagctgca	gagcgagcca	gagcgtgagc	agcagctatc	tggcgtggta	ccagcagaaa	120
ccaggtcaag	caccgcgtct	attaatttat	ggcgcgagca	gccgtgcaac	tggggccccg	180
gcgcgtttta	gcggctctgg	atccggcacg	gattttaccc	tgaccattag	cagcctggaa	240
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cagggtagca	aagttgaaat	taaacgtacg	gtggctgctc	cgagcgtggt	tatttttccg	360
ccgagcgatg	aacaactgaa	aagcggcacg	gcgagcgtgg	tgtgcctgct	gaacaacttt	420
tatccgcgtg	aagegaaagt	tcagtggaaa	gtagacaacg	cgctgcaaag	cggcaacagc	480
caggaaagcg	tgaccgaaca	ggatagcaaa	gatagcacct	attctctgag	cagcacctcg	540
accctgagca	tgaaaaacat	aaagtgtatg	cgctgcgaagt	gacccatcaa		600
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<210> 345

<211> 649

<212> DNA

<213> Homo sapiens

<400> 345

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gcagcatccc	gggaaggcgc	cgaaactgat	gatttatgat	gtgagcaacc	gtccctcagg	180
cgtgagcaac	cgtttttagcg	gatccaaaag	cggcaacacc	gcgagcctga	ccattagcgg	240
cctgcaagcg	gaagacgaag	cggattatta	ttgccagagc	tatgacattt	ctggttatcc	300
tgtgtttggc	ggcggcacga	agttaaccgt	tcttgccag	ccgaaagccg	caccgagtgt	360
gacgctgttt	ccgccgagca	gcgaagaatt	gcaggcgaac	aaagcgaccc	tggtgtgcct	420
gattagcgac	ttttatccgg	gagccgtgac	agtggcctgg	aaggcagata	gcagccccgt	480
caaggcggga	gtggagacca	ccacaccctc	caaacaaagc	aacaacaagt	acgcggccag	540
cagctatctg	agcctgacgc	ctgagcagtg	gaagtcccac	agaagctaca	gctgccaggt	600
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<210> 346

<211> 648

<212> DNA

<213> Homo sapiens

<400> 346

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catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag	acgaagcgga	ttattattgc	cagagccgtg	acctttatta	tgtttattat	300
gtgtttggcg	gcggcacgaa	gttaaccgtt	cttgccagc	cgaaagccgc	accgagtgtg	360
acgctgtttc	cgccgagcag	cgaagaattg	caggcgaaca	aagcgaccct	ggtgtgcctg	420
attagcgact	tttatccggg	agccgtgaca	gtggcctgga	aggcagatag	cagccccgtc	480
aaggcgggag	tggagaccac	cacaccctcc	aaacaaagca	acaacaagta	cgcgcccgagc	540
agctatctga	gcctgacgcc	tgagcagtg	aagtcaccaca	gaagctacag	ctgccaggtc	600

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648

<210> 347

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<212> DNA

<213> Homo sapiens

<400> 347

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caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcgga	240
gacgaagcgg	attattattg	ccagagctat	gaccgttcta	tgtgggtgtt	tggcgggcg	300
acgaagttaa	ccgttcttgg	ccagccgaaa	gccgcaccga	gtgtgacgct	gtttccgccg	360
agcagcgaag	aattgcaggc	gaacaaagcg	accctggtgt	gcctgattag	cgacttttat	420
ccgggagccg	tgacagtggc	ctggaaggca	gatagcagcc	ccgtcaaggc	gggagtggag	480
accaccacac	cctccaaaca	aagcaacaac	aagtacgcgg	ccagcagcta	tctgagcctg	540
acgcctgagc	agtggaaagtc	ccacagaagc	tacagctgcc	aggtcacgca	tgaggggagc	600
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<211> 645

<212> DNA

<213> Homo sapiens

<400> 348

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tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
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<211> 636

<212> DNA

<213> Homo sapiens

<400> 349

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caggcgccag	ttctggtgat	ttatgatgat	tctgaccgtc	cctcaggcat	cccggaaacgc	180
tttagcggat	ccaacagcgg	caacaccgcg	accctgacca	ttagcggcac	tcaggcgga	240
gacgaagcgg	attattattg	ccagagctgg	gacccttctc	attattatgt	gtttggcggc	300
ggcacgaagt	taaccgttct	tggccagccg	aaagccgcac	cgagtgtgac	gctgtttccg	360

ccgagcagcg	aagaattgca	ggcgaacaaa	gcgaccctgg	tgtgcctgat	tagcgacttt	420
tatccgggag	ccgtgacagt	ggcctggaag	gcagatagca	gccccgtcaa	ggcgggagtg	480
gagaccacca	caccctccaa	acaaagcaac	aacaagtacg	cggccagcag	ctatctgagc	540
ctgacgcctg	agcagtggaa	gtcccacaga	agctacagct	gccaggtcac	gcatgagggg	600
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<210> 350

<211> 645

<212> DNA

<213> Homo sapiens

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catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
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caagcgggaag	acgaagcggga	ttattattgc	cagagctatg	acattatgcc	tgagcgtgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc	cgagcagcga	agaattgcag	gcgaacaaag	cgaccctggt	gtgcctgatt	420
agcgactttt	atccggggagc	cgtgacagt	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
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<213> Homo sapiens

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catcccggga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
agcaaccgtt	ttagcggatc	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcgggaag	acgaagcggga	ttattattgc	cagagcatgg	actttcgtct	tatgcatgtg	300
tttggcggcg	gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
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gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
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<212> DNA

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catcccgga	aggcgccgaa	actgatgatt	tatgatgtga	gcaaccgtcc	ctcaggcgtg	180
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agcgactttt	atccggggagc	cgtgacagtg	gcctggaagg	cagatagcag	ccccgtcaag	480
gcgggagtg	agaccaccac	accctccaaa	caaagcaaca	acaagtacgc	ggccagcagc	540
tatctgagcc	tgacgcctga	gcagtggaa	tcccacagaa	gctacagctg	ccaggtcacg	600
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<212> DNA

<213> Homo sapiens

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Gly Phe Thr Phe Asn Ser Tyr Ala Met Ser
1 5 10

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<213> Homo sapiens

<400> 357

Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15
Gly

<210> 358

<211> 17

<212> PRT

<213> Homo sapiens

<400> 358

Val Ile Ser Gly Asn Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15
Gly

<210> 359

<211> 17

<212> PRT

<213> Homo sapiens

<400> 359

Gly Ile Ser Gly Asn Gly Val Leu Ile Phe Tyr Ala Asp Ser Val Lys
1 5 10 15
Gly

<210> 360

<211> 5

<212> PRT

<213> Homo sapiens

<400> 360

Gly Leu Met Asp Tyr
1 5

<210> 361

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<400> 361

Trp Phe Asp His
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Trp Phe Asp Val
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Asp Val Ser Asn Arg Pro Ser
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Gln Ser Tyr Asp Phe Ile Arg Phe Met
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Gly Gly Thr Phe Ser Ser Tyr Ala Ile Ser
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Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Gly
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<400> 368
Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
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Gly

<210> 369
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Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
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Gly

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Trp Ser Asp Gln Ser Tyr His Tyr Tyr Trp His Pro Tyr Phe Asp Val
1 5 10 15

<210> 371
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Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Ser
1 5 10

<210> 372
<211> 14
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<400> 372
Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 373
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<400> 373
Leu Met Ile Tyr Asp Asn Asn Gln Arg Pro Ser
1 5 10

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Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser
1 5 10

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Leu Met Ile Tyr Ala Gly Asn Asn Arg Pro Ser
1 5 10

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<400> 376

Gln Ala Phe Asp Val Ala Pro Asn Gly Lys
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<210> 377

<211> 10

<212> PRT

<213> Homo sapiens

<400> 377

Gln Ala Phe Ala Val Met Pro Asn Val Glu
1 5 10

<210> 378

<211> 10

<212> PRT

<213> Homo sapiens

<400> 378

Gln Ser Phe Thr Val Ser Pro Gly Ala Asp
1 5 10

<210> 379

<211> 9

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<400> 379

Gln Ala Tyr Asp Ser Ser Gly Tyr Pro
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<210> 381

<211> 43

<212> DNA

<213> Homo sapiens

<400> 381

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43

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